PB87-142998

Air Quality Criteria for Ozone and Other Photochemical Oxidants. Volume 5

(U.S.) Environmental Protection Agency
Research Triangle Park, NC

Aug 86

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National Technical Information Service
NTIS

TECHNICAL REPORT DATA
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1. REPORT NO. EPA/600/8-84/020eF	**2.**	**3. RECIPIENT'S ACCESSION NO.** PB87 142998/AS
4. TITLE AND SUBTITLE Air Quality Criteria for Ozone and Other Photochemical Oxidants. Volume V of V		**5. REPORT DATE** August 1986 **6. PERFORMING ORGANIZATION CODE** EPA/600/23
7. AUTHOR(S)		**8. PERFORMING ORGANIZATION REPORT NO.**
9. PERFORMING ORGANIZATION NAME AND ADDRESS Environmental Criteria and Assessment Office (MD-52) Office of Health and Environmental Assessment (ORD) U.S. Environmental Protection Agency Research Triangle Park, N.C. 27711		**10. PROGRAM ELEMENT NO.** **11. CONTRACT/GRANT NO.**
12. SPONSORING AGENCY NAME AND ADDRESS Office of Health and Environmental Assessment Office of Research and Development U.S. Environmental Protection Agency Washington, D.C. 20460		**13. TYPE OF REPORT AND PERIOD COVERED** Air Quality Criteria **14. SPONSORING AGENCY CODE** EPA/600/21

15. SUPPLEMENTARY NOTES

16. ABSTRACT

Selected scientific information through early 1986 is presented and evaluated relative to the health and welfare effects associated with exposure to ozone and other photochemical oxidants.

Data on health and welfare effects are emphasized; additional information is provided for understanding the oxidant pollution problem, for evaluating the reliability of effects data, and for assessing effects data relative to concentrations occurring in ambient air. Information is also presented on exposure-related topics: sources, measurement, and concentrations of oxidant precursors; formation and transport of ozone and other photochemical oxidants; properties, chemistry, and measurement of ozone and other photochemical oxidants; and the concentrations of ozone and other photochemical oxidants typically found in ambient air.

The specific areas addressed by chapters on health and welfare effects are the toxicological appraisal of effects of ozone and other oxidants; effects observed in controlled human exposures; effects observed in field and epidemiological studies; and effects on vegetation, natural and agroecosystems, and nonbiological materials.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Release to Public	**19. SECURITY CLASS** *(This Report)* Unclassified	**21. NO. OF PAGES** 328
	20. SECURITY CLASS *(This page)* Unclassified	**22. PRICE**

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

United States
Environmental Protection
Agency

Environmental Criteria and
Assessment Office
Research Triangle Park, NC 27711

EPA/600/8-84/020eF
August 1986

PB87-142998

Research and Development

EPA

Air Quality Criteria for Ozone and Other Photochemical Oxidants

Volume V of V

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

EPA/600/8-84/020eF
August 1986

Air Quality Criteria for Ozone and Other Photochemical Oxidants

Volume V of V

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, N.C. 27711

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ABSTRACT

Scientific information is presented and evaluated relative to the health and welfare effects associated with exposure to ozone and other photochemical oxidants. Although it is not intended as a complete and detailed literature review, the document covers pertinent literature through early 1986.

Data on health and welfare effects are emphasized, but additional information is provided for understanding the nature of the oxidant pollution problem and for evaluating the reliability of effects data as well as their relevance to potential exposures to ozone and other oxidants at concentrations occurring in ambient air. Information is provided on the following exposure-related topics: nature, source, measurement, and concentrations of precursors to ozone and other photochemical oxidants; the formation of ozone and other photochemical oxidants and their transport once formed; the properties, chemistry, and measurement of ozone and other photochemical oxidants; and the concentrations of ozone and other photochemical oxidants that are typically found in ambient air.

The specific areas addressed by chapters on health and welfare effects are the toxicological appraisal of effects of ozone and other oxidants; effects observed in controlled human exposures; effects observed in field and epidemiological studies; effects on vegetation seen in field and controlled exposures; effects on natural and agroecosystems; and effects on nonbiological materials observed in field and chamber studies.

AIR QUALITY CRITERIA FOR OZONE AND OTHER PHOTOCHEMICAL OXIDANTS

Page

VOLUME I
Chapter 1. Summary and Conclusions 1-1

VOLUME II
Chapter 2. Introduction 2-1
Chapter 3. Properties, Chemistry, and Transport of Ozone and Other Photochemical Oxidants and Their Precursors 3-1
Chapter 4. Sampling and Measurement of Ozone and Other Photochemical Oxidants and Their Precursors 4-1
Chapter 5. Concentrations of Ozone and Other Photochemical Oxidants in Ambient Air 5-1

VOLUME III
Chapter 6. Effects of Ozone and Other Photochemical Oxidants on Vegetation 6-1
Chapter 7. Effects of Ozone on Natural Ecosystems and Their Components 7-1
Chapter 8. Effects of Ozone and Other Photochemical Oxidants on Nonbiological Materials 8-1

VOLUME IV
Chapter 9. Toxicological Effects of Ozone and Other Photochemical Oxidants 9-1

VOLUME V
Chapter 10. Controlled Human Studies of the Effects of Ozone and Other Photochemical Oxidants 10-1
Chapter 11. Field and Epidemiological Studies of the Effects of Ozone and Other Photochemical Oxidants 11-1
Chapter 12. Evaluation of Health Effects Data for Ozone and Other Photochemical Oxidants 12-1

TABLE OF CONTENTS

Page

LIST OF TABLES viii
LIST OF FIGURES x
LIST OF ABBREVIATIONS xii
AUTHORS, CONTRIBUTORS, AND REVIEWERS xvii

10. CONTROLLED HUMAN STUDIES OF THE EFFECTS OF OZONE AND OTHER PHOTOCHEMICAL OXIDANTS 10-1
  10.1 INTRODUCTION 10-1
  10.2 ACUTE PULMONARY EFFECTS OF OZONE 10-6
    10.2.1 Introduction 10-6
    10.2.2 At-Rest Exposures 10-7
    10.2.3 Exposures with Exercise 10-7
    10.2.4 Intersubject Variability and Reproducibility of Responses 10-22
    10.2.5 Prediction of Acute Pulmonary Effects 10-25
    10.2.6 Bronchial Reactivity 10-28
    10.2.7 Mechanisms of Acute Pulmonary Effects 10-30
    10.2.8 Preexisting Disease 10-32
    10.2.9 Other Factors Affecting Pulmonary Responses to Ozone 10-38
      10.2.9.1 Cigarette Smoking 10-38
      10.2.9.2 Age and Sex Differences 10-41
      10.2.9.3 Environmental Conditions 10-44
      10.2.9.4 Vitamin E Supplementation 10-45
  10.3 PULMONARY EFFECTS FOLLOWING REPEATED EXPOSURE TO OZONE 10-47
  10.4 EFFECTS OF OZONE ON VIGILANCE AND EXERCISE PERFORMANCE 10-60
  10.5 INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS 10-65
    10.5.1 Ozone Plus Sulfates or Sulfuric Acid 10-65
    10.5.2 Ozone and Carbon Monoxide 10-74
    10.5.3 Ozone and Nitrogen Dioxide 10-74
    10.5.4 Ozone and Other Mixed Pollutants 10-76
  10.6 EXTRAPULMONARY EFFECTS OF OZONE 10-77
  10.7 PEROXYACETYL NITRATE 10-84
  10.8 SUMMARY 10-87
  10.9 REFERENCES 10-97

11. FIELD AND EPIDEMIOLOGICAL STUDIES OF THE EFFECTS OF OZONE AND OTHER PHOTOCHECMICAL OXIDANTS 11-1
  11.1 INTRODUCTION 11-1
  11.2 FIELD STUDIES OF EFFECTS OF ACUTE EXPOSURE TO OZONE AND OTHER PHOTOCHEMICAL OXIDANTS 11-2
    11.2.1 Symptoms and Pulmonary Function in Field Studies of Ambient Air Exposures 11-3
    11.2.2 Symptoms and Pulmonary Function in Field or Simulated High-Altitude Studies 11-12
  11.3 EPIDEMIOLOGICAL STUDIES OF EFFECTS OF ACUTE EXPOSURE 11-13
    11.3.1 Acute Exposure Morbidity Effects 11-13

TABLE OF CONTENTS (continued)

Page

11.3.1.1 Symptom Aggravation in Healthy Populations 11-13
11.3.1.2 Altered Performance 11-14
11.3.1.3 Acute Effects on Pulmonary Function 11-14
11.3.1.4 Aggravation of Existing Respiratory Diseases 11-24
11.3.1.5 Incidence of Acute Respiratory Illness 11-34
11.3.1.6 Physician, Emergency Room, and Hospital Visits 11-34
11.3.1.7 Occupational Studies 11-40
11.3.2 Trends in Mortality 11-40
11.4 EPIDEMIOLOGICAL STUDIES OF EFFECTS OF CHRONIC EXPOSURE 11-40
11.4.1 Pulmonary Function and Chronic Lung Disease 11-44
11.4.2 Chromosomal Effects 11-48
11.4.3 Chronic Disease Mortality 11-49
11.5 SUMMARY AND CONCLUSIONS 11-49
11.6 REFERENCES 11-55

12. EVALUATION OF HEALTH EFFECTS DATA FOR OZONE AND OTHER PHOTOCHEMICAL OXIDANTS 12-1
12.1 INTRODUCTION 12-1
12.2 EXPOSURE ASPECTS 12-5
12.2.1 Potential Exposures to Ozone 12-5
12.2.2 Potential Exposures to Other Photochemical Oxidants 12-11
12.2.2.1 Concentrations 12-11
12.2.2.2 Patterns 12-14
12.2.3 Potential Combined Exposures and Relationship of Ozone and Other Photochemical Oxidants 12-14
12.3 HEALTH EFFECTS IN THE GENERAL HUMAN POPULATION 12-17
12.3.1 Clinical Symptoms 12-17
12.3.2 Pulmonary Function at Rest and with Exercise and Other Stresses 12-19
12.3.2.1 At-Rest Exposures 12-19
12.3.2.2 Exposures with Exercise 12-21
12.3.2.3 Environmental Stresses 12-35
12.3.3 Other Factors Affecting Pulmonary Response to Ozone 12-35
12.3.3.1 Age 12-35
12.3.3.2 Sex 12-36
12.3.3.3 Smoking Status 12-37
12.3.3.4 Nutritional Status 12-37
12.3.3.5 Red Blood Cell Enzyme Deficiencies 12-39
12.3.4 Effects of Repeated Exposure to Ozone 12-40
12.3.4.1 Introduction 12-40
12.3.4.2 Development of Altered Responsiveness to Ozone 12-40

TABLE OF CONTENTS (continued)

Page

12.3.4.3 Conclusions Relative to Attenuation with Repeated Exposures 12-41
12.3.5 Mechanisms of Responsiveness to Ozone 12-42
12.3.6 Relationship Between Acute and Chronic Ozone Effects 12-45
12.3.7 Resistance to Infection 12-49
12.3.8 Extrapulmonary Effects of Ozone 12-50
12.4 HEALTH EFFECTS IN INDIVIDUALS WITH PREEXISTING DISEASE 12-53
12.4.1 Patients with Chronic Obstructive Lung Disease (COLD) 12-53
12.4.2 Asthmatics 12-54
12.4.3 Subjects with Allergy, Atopy, and Ozone-Induced Hyperreactivity 12-56
12.5 EXTRAPOLATION OF EFFECTS OBSERVED IN ANIMALS TO HUMAN POPULATIONS 12-57
12.5.1 Species Comparisons 12-57
12.5.2 Dosimetry Modeling 12-63
12.6 HEALTH EFFECTS OF OTHER PHOTOCHEMICAL OXIDANTS AND POLLUTANT MIXTURES 12-65
12.6.1 Effects of Peroxyacetyl Nitrate 12-65
12.6.2 Effects of Hydrogen Peroxide 12-66
12.6.3 Interactions with Other Pollutants 12-67
12.7 IDENTIFICATION OF POTENTIALLY AT-RISK GROUPS 12-69
12.7.1 Introduction 12-69
12.7.2 Potentially At-Risk Individuals 12-69
12.7.3 Potentially At-Risk Groups 12-72
12.7.4 Demographic Distribution of the General Population 12-75
12.7.5 Demographic Distribution of Individuals with Chronic Respiratory Conditions 12-76
12.8 SUMMARY AND CONCLUSIONS 12-78
12.8.1 Health Effects in the General Human Population 12-78
12.8.2 Health Effects in Individuals with Preexisting Disease 12-86
12.8.3 Extrapolation of Effects Observed in Animals to Human Populations 12-86
12.8.4 Health Effects of Other Photochemical Oxidants and Pollutant Mixtures 12-87
12.8.5 Identification of Potentially At-Risk Groups 12-88
12.9 REFERENCES 12-90

APPENDIX A A-1

LIST OF TABLES

Table Page

10-1 Human experimental exposure to ozone up to 1978 10-2
10-2 Studies on acute pulmonary effects of ozone since 1978 10-8
10-3 Estimated values of oxygen consumption and minute ventilation associated with representative types of exercise 10-14
10-4 Ozone exposure in subjects with pulmonary disease 10-33
10-5 Changes in lung function after repeated daily exposure to ambient ozone 10-48
10-6 Effects of ozone on exercise performance 10-64
10-7 Interactions between ozone and other pollutants 10-66
10-8 Human extrapulmonary effects of ozone exposure 10-78
10-9 Acute human exposure to peroxyacetyl nitrate 10-85
10-10 Summary table: controlled human exposure to ozone 10-88

11-1 Subject characteristics and experimental conditions in the mobile laboratory studies 11-4
11-2 Symptom aggravation in health populations exposed to photochemical oxidant pollution 11-15
11-3 Altered performance associated with exposure to photochemical oxidant pollution 11-17
11-4 Acute effects of photochemical oxidant pollution on pulmonary function of children and adults 11-18
11-5 Aggravation of existing respiratory diseases by photochemical oxidant pollution 11-25
11-6 Incidence of acute respiratory illness associated with photochemical oxidant pollution 11-35
11-7 Hospital admissions in relation to photochemical oxidant pollution 11-36
11-8 Acute effects from occupational exposure to photochemical oxidants 11-41
11-9 Daily mortality associated with exposure to photochemical oxidant pollution 11-43
11-10 Pulmonary function effects associated with chronic photochemical oxidant exposure 11-45
11-11 Summary table: acute effects of ozone and other photochemical oxidants in field studies with a mobile laboratory .. 11-51

12-1 Number of times the daily maximum 1-hr ozone concentration was ≥0.06, ≥0.12, ≥0.18, and ≥0.24 ppm for specified consecutive days in Pasadena, Dallas, and Washington, April through September, 1979 through 1981 12-9
12-2 Relationship of ozone and peroxyacetyl nitrate at urban and suburban sites in the United States in reports published 1978 or later 12-16
12-3 Effects of intermittent exercise and ozone concentration on 1-sec forced expiratory volume during 2-hr exposures 12-29
12-4 Comparison of the acute effects of ozone on breathing patterns in animals and man 12-60

LIST OF TABLES (continued)

Table		Page
12-5	Comparison of the acute effects of ozone on airway reactivity in animals and man	12-61
12-6	Geographical distribution of the resident population of the United States, 1980	12-77
12-7	Total population of the United States by age, sex, and race, 1980	12-78
12-8	Prevalence of chronic respiratory conditions by sex and age for 1979	12-79

LIST OF FIGURES

Figure | Page

10-1 Change in forced vital capacity (FVC), forced expiratory volume in 1-sec ($FEV_{1.0}$), and maximal mid-expiratory flow ($FEF_{25-75\%}$) during exposure to filtered air or ozone (0.5 ppm) for 2 hr. Exercise at 45% maximal aerobic capacity (max $\dot{V}O_2$) was performed for 30 min by Group A after 60 min of ozone exposure and by Group B after 30 min of ozone exposure 10-16

10-2 Frequency distributions of response (percent change from baseline) in specific airway resistance (SR_{aw}) and forced expiratory volume in 1-sec ($FEV_{1.0}$) for individuals exposed to six levels of ozone. One individual with 260% increase in SR_{aw} exposed to 0.4 ppm ozone is not graphed 10-23

10-3 Forced expiratory volume in 1-sec ($FEV_{1.0}$) in two groups of subjects exposed to (A) 0.35 ppm ozone, and (B) 0.50 ppm ozone, for 3 successive days. Numbers on the abscissa represent successive half-hour periods of exposure 10-52

10-4 Percent change (pre-post) in 1-sec forced expiratory volume ($FEV_{1.0}$), as the result of a 2-hr exposure to 0.42 ppm ozone. Subjects were exposed to filtered air, to ozone for five consecutive days, and exposed to ozone again: (A) 1 week later; (B) 2 weeks later; and (C) 3 weeks later 10-54

11-1 Changes in mean symptom score with exposure for all subjects, for normal and allergic subjects, and for asthmatic subjects 11-7

11-2 Changes in group mean responses, including $FEV_{1.0}$, symptoms, and exercise performance in 50 competitive cyclists exercising continuously for 1 hr while exposed to ozone 11-10

12-1 Distributions of the three highest 1-hr ozone concentrations at valid sites (906 station-years) aggregated for 3 years (1979, 1980, and 1981) and the highest ozone concentrations at NAPBN sites aggregated for those years (24 station-years) 12-7

12-2 The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with light intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits 12-25

12-3 The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with moderate intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits 12-26

LIST OF FIGURES (continued)

Figure Page

12-4 The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with heavy intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits 12-27

12-5 The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with very heavy intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits 12-28

12-6 Group mean decrements in 1-sec forced expiratory volume during 2-hr ozone exposures with different levels of intermittent exercise: light ($\dot{V}_E \leq 23$ L/min); moderate ($\dot{V}_E = 24\text{-}43$ L/min); heavy ($\dot{V}_E = 44\text{-}63$ L/min); and very heavy ($\dot{V}_E \geq 64$ L/min) 12-81

LIST OF ABBREVIATIONS

ACh	Acetylcholine
AM	Alveolar macrophage
ANOVA	Analysis of variance
AOD	Airway obstructive disease
ATPS	ATPS condition (ambient temperature and pressure, saturated with water vapor)
BTPS	BTPS conditions (body temperature, barometric pressure, and saturated with water vapor)
CC	Closing capacity
C_{dyn}	Dynamic lung compliance
CE	Continuous exercise
CHEM	Gas-phase chemiluminescence
CHESS	Community Health Environmental Surveillance System
C_L	Lung compliance
C_{Lst}	Static lung compliance
CNS	Central nervous system
CO	Carbon monoxide
COHb	Carboxyhemoglobin
COLD	Chronic obstructive lung disease
COPD	Chronic obstructive pulmonary disease
CO_2	Carbon dioxide
CV	Closing volume
D_L	Diffusing capacity of the lungs
D_{LCO}	Carbon monoxide diffusing capacity of the lungs
E	Elastance
ECG, EKG	Electrocardiogram
EEG	Electroencephalogram
EPA	U.S. Environmental Protection Agency
ERV	Expiratory reserve volume
FEF_{max}	Maximal forced expiratory flow achieved during an FVC test
FEF	Forced expiratory flow

LIST OF ABBREVIATIONS (continued)

$\mathrm{FEF}_{200-1200}$	Mean forced expiratory flow between 200 ml and 1200 ml of the FVC [formerly called the maximum expiratory flow rate (MEFR)]
$\mathrm{FEF}_{25-75\%}$	Mean forced expiratory flow during the middle half of the FVC [formerly called the maximum mid-expiratory flow rate (MMFR)]
$\mathrm{FEF}_{75\%}$	Instantaneous forced expiratory flow after 75% of the FVC has been exhaled
FEV	Forced expiratory volume
FEV_1	Forced expiratory volume in 1 sec
$\mathrm{FEV}_t/\mathrm{FVC}$	A ratio of timed forced expiratory volume (FEV_t) to forced vital capacity (FVC)
FIVC	Forced inspiratory vital capacity
f_R	Respiratory frequency
FRC	Functional residual capacity
FVC	Forced vital capacity
G	Conductance
G-6-PD	Glucose-6-phosphate dehydrogenase
Gaw	Airway conductance
GS-CHEM	Gas-solid chemiluminescence
GSH	Glutathione
Hb	Hemoglobin
Hct	Hematocrit
$\mathrm{HO}\cdot$	Hydroxy radical
$\mathrm{HO}_2\cdot$	Hydroperoxy radical
IC	Inspiratory capacity
IE	Intermittent exercise
IRV	Inspiratory reserve volume
IVC	Inspiratory vital capacity
LDH	Lactate deyhydrogenase
LD_{50}	Lethal dose (50 percent)
LM	Light microscopy
MAST	KI-coulometric (Mast meter)

LIST OF ABBREVIATIONS (continued)

max $\dot{V}_E$	Maximum ventilation
max $\dot{V}O_2$	Maximal aerobic capacity
MBC	Maximum breathing capacity
MEFR	Maximum expiratory flow rate
MetHb	Methemoglobin
MMAD	Mass median aerodynamic diameter
MMFR or MMEF	Maximum mid-expiratory flow rate
MVV	Maximum voluntary ventilation
NBKI	Neutral buffered potassium iodide
$(NH_4)_2SO_4$	Ammonium sulfate
NO_2	Nitrogen dioxide
ΔN_2, dN_2	Nitrogen washout
O_2	Oxygen
O_2-	Oxygen radical
O_3	Ozone
$P(A-a)O_2$	Alveolar-arterial oxygen pressure difference
PABA	para-aminobenzoic acid
P_ACO_2	Alveolar partial pressure of carbon dioxide
$PaCO_2$	Arterial partial pressure of carbon dioxide
PAN	Peroxyacetyl nitrate
P_AO_2	Alveolar partial pressure of oxygen
PaO_2	Arterial partial pressure of oxygen
PBzN	Peroxybenzoyl nitrate
PEF	Peak expiratory flow
PEFV	Partial expiratory flow-volume curve
PG	Prostaglandin
pH_a	Arterial pH
P_L	Transpulmonary pressure
PMN	Polymorphonuclear leukocyte
P_{st}	Static transpulmonary pressure
PUFA	Polyunsaturated fatty acid
R	Resistance to flow

LIST OF ABBREVIATIONS (continued)

Raw	Airway resistance
RBC	Red blood cell
R_{coll}	Collateral resistance
rh	Relative humidity
R_L	Total pulmonary resistance
RQ, R	Respiratory quotient
R_t	Respiratory resistance
R_{ti}	Tissue resistance
RV	Residual volume
SaO_2	Arterial oxygen saturation
SBNT	Single-breath nitrogen test
SBP	Systolic blood pressure
SCE	Sister chromatid exchange
Se	Selenium
SEM	Scanning electron microscopy
SGaw	Specific airway conductance
SH	Sulfhydryls
SOD	Superoxide dismutase
SO_2	Sulfur dioxide
SO_4	Sulfate
SPF	Specific pathogen-free
SRaw	Specific airway resistance
STPD	STPD conditions (standard temperature and pressure, dry)
TEM	Transmission electron microscopy
TGV	Thoracic gas volume
THC	Total hydrocarbons
TLC	Total lung capacity
TV	Tidal volume
UV	Ultraviolet photometry
$\dot{V}_A$	Alveolar ventilation
$\dot{V}_A/\dot{Q}$	Ventilation/perfusion ratio
VC	Vital capacity

LIST OF ABBREVIATIONS (continued)

$\dot{V}CO_2$	Carbon dioxide production
V_D	Physiological dead space
$\dot{V}_D$	Dead-space ventilation
$V_{D\ anat}$	Anatomical dead space
$\dot{V}_E$	Minute ventilation; expired volume per minute
$\dot{V}_I$	Inspired volume per minute
V_L	Lung volume
$\dot{V}_{max}$	Maximum expiratory flow
$\dot{V}O_2$	Oxygen uptake
$\dot{V}O_2$, $\dot{Q}O_2$	Oxygen consumption

MEASUREMENT ABBREVIATIONS

g	gram
hr/day	hours per day
kg	kilogram
kg-m/min	kilogram-meter/min
L/min	liters/min
L/s	liters/sec
ppm	parts per million
mg/kg	milligrams per kilogram
mg/m^3	milligrams per cubic meter
min	minute
ml	milliliter
mm	millimeter
$\mu g/m^3$	micrograms per cubic meter
µm	micrometer
µM	micromole
sec	second

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10. CONTROLLED HUMAN STUDIES OF THE EFFECTS OF OZONE AND OTHER PHOTOCHEMICAL OXIDANTS

10.1 INTRODUCTION

Four major summaries on the effects of controlled human exposure to ozone (O_3) have been published (National Research Council, 1977; U.S. Environmental Protection Agency, 1978; World Health Organization, 1978; and Hughes, 1979). In addition, two other reports (National Air Pollution Control Administration, 1970; F.R. April 30, 1971) have reviewed earlier studies.

In 1977 the National Research Council report on ozone and other photochemical oxidants stated a need for comprehensive human experimental studies that were carefully controlled and documented to ensure reproducibility. This statement was understandable, considering that the major portion of the report's section on controlled human studies was devoted to reviews of test methods, protocol designs, review of a scant amount of published data, and recommendations for future studies. The available data on controlled studies through 1975 were limited to some 20 publications. Nonetheless, this data base represented a substantial increase above the information available prior to 1970, and it became evident that exposure to O_3 at low ambient concentrations resulted in some degree of pulmonary dysfunction. Additional research was conducted in the intervening years, and by 1978 data were available from studies conducted on over 200 individuals (Table 10-1). By this time the first reports were available indicating that under the same exposure conditions, greater functional deficits were measured during exercise than at rest. In addition, five studies in which several pollutants (nitrogen dioxide, sulfur dioxide, and carbon monoxide plus oxidants) were present during exposure became available for review. Two reports on repeated daily exposure to O_3 ("adaptation") had appeared, as well as one experimental study in which asthmatics were evaluated. This research was just the beginning of interest in O_3 as an ambient pollutant affecting pulmonary functions of exposed man. Although the data base was still smaller than desirable, a general conception of this particular air pollutant's influence was beginning to form.

The early reports summarized in Table 10-1 were described in detail in the previous O_3 criteria document (U.S. Environmental Protection Agency, 1978). In this chapter, emphasis has been placed on the more recent literature; however, some of the older studies have been reviewed again. Tables

TABLE 10-1. HUMAN EXPERIMENTAL EXPOSURE TO OZONE UP TO 1978

Ozone concentration µg/m^3	Ozone concentration ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
196	0.10	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	P(A-a)O_2 and R_{aw} increased; PaO_2 decreased. Results questionable.	12 male	von Nieding et al., 1977
196 784 1176 1960	0.1 0.4 0.6 1.0	I	1 hr R	Airway resistance: mean increases of 3.3% (0.1 ppm), 3.5% (0.4 ppm), 5.8% (0.6 ppm), and 19.3% (1.0 ppm) at 0 hr after exposure; mean increases of 12.5% (0.4 ppm), 5% (0.6 and 1.0 ppm) at 1 hr after exposure; one subject had history of asthma and experienced hemoptysis 2 days after 1 ppm. No symptoms at 0.1 ppm; odor detected at 0.4 and 0.6 ppm; throat irritation and cough at 1.0 ppm.	4 male	Goldsmith and Nadel, 1969
294 588	0.15 0.30	UV, NBKI	1 hr (mouthpiece) R (11) & CE (29, 43, 66)	RV, $FEV_{1.0}$, MMFR, and V_T decreased and f_B increased at 0.30 ppm during IE (66); small but nonsignificant changes at 0.15 ppm. Congestion, wheezing, and headache reported.	6 male	DeLucia and Adams, 1977
392 980	0.2 0.5	I	3 hr/day 6 days/week x 12 weeks	Slight (nonsignificant) decrease in VC and significant decrease in $FEV_{1.0}$ at 0.5 ppm toward end of 12 weeks; returned to normal within 6 weeks after exposure; 0.66 (0.2 ppm), 0.80 (0.5 ppm) upper respiratory infections/person in 12 weeks compared to 0.95 for the controls. No irritating symptoms, but could detect ozone by smell at 0.5 ppm.	6 male	Bennett, 1962
451	0.23	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No changes in spirometry, closing volume, and N_2 washout; small blood biochemical changes; increased frequency of symptoms reported. Medication maintained during exposure.	20 male (asthma) 2 female (asthma)	Linn et al., 1978
490 725 980	0.25 0.37 0.50	CHEM, NBKI	2-4 hr R & IE (2xR) @ 15-min intervals	No effect in normal reactors. Changes (2-12%) observed in spirometry, lung mechanics, and small airway function in non-reactors (IE) and hyperreactors (R) at 0.5 ppm.	16 normal and reactive subjects	Hackney et al., 1975a,b,c

TABLE 10-1 (continued). HUMAN EXPERIMENTAL EXPOSURE TO OZONE UP TO 1978

Ozone concentration $\mu g/m^3$	Ozone concentration ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
725	0.37	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No changes in spirometry or small airway function in the combined group; sensitive subjects had decreased $FEV_{1.0}$ (4.7%).	4 normal (L.A.) 4 sensitive (L.A.)	Bell et al., 1977
725	0.37	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No changes in group mean pulmonary function; individual subjective symptoms and spirometric decrements were more severe in Toronto than L.A. subjects. Blood enzyme activity increased in both groups, but RBC fragility increased in Toronto subjects only.	2 male (Toronto) 2 female (Toronto) 3 male (L.A.) 1 female (L.A.)	Hackney et al., 1977b
725 1470	0.37 0.75	MAST, NBKI	2 hr IE (2xR) @ 15-min intervals	At 0.37 ppm, less than 20% decrements in spirometry. Smokers less responsive than nonsmokers. At 0.75 ppm, severe decrements in spirometric variables (20%-55%). Smokers more responsive, with RV and CC increased.	12 male	Bates and Hazucha, 1973 Hazucha et al., 1973 Hazucha, 1973
725 980 1470	0.37 0.50 0.75	MAST, NBKI	2 hr R (11) & IE (29) @ 15-min intervals	0.75 ppm: at rest, less than 21% decrements in spirometry, while during IE nearly 33% decrements in spirometry and dN_2. Relatively smaller effects at lower concentrations. Reasonably good correlation between dose (conc. x min. vent.) and changes in spirometric variables.	20 male 8 female (divided into 6 exposure groups)	Silverman et al., 1976
725 980 1470	0.37 0.50 0.75	MAST, NBKI	2 hr R (11) & IE (29) @ 15-min intervals	f_B increased and V_T decreased with exercise; $\dot{V}O_2$ not affected by exposure. Variables correlated to total dose of ozone.	20 male 8 female (divided into 6 exposure groups)	Folinsbee et al., 1975
784	0.4	CHEM, NBKI	1-4 hr IE (4xR) for two 15-min periods	FVC and MMEF decreased and R_{aw} increased at 2 hr and 4 hr; $FEV_{1.0}$, $\dot{V}_{50}$, and $\dot{V}_{25}$ decreased at 4 hr only.	22 male	Knelson et al., 1976
784	0.4	CHEM, NBKI	2.25 hr IE (2xR) @ 15-min intervals	FVC, $FEV_{1.0}$, and MMF decreased in new arrivals, which were more responsive than L.A. residents. Inconsistent changes in blood biochemistry.	6 female (L.A.) 7 female (new arrival) 2 male (new arrival)	Hackney et al., 1976
980	0.5	CHEM, NBKI	4 days 2.5 hr/day IE (2xR) @ 15-min intervals	Very small changes in pulmonary function; temporal pattern of these changes is suggestive of "adaptation."	6 male (atopic)	Hackney et al., 1977a

TABLE 10-1 (continued). HUMAN EXPERIMENTAL EXPOSURE TO OZONE UP TO 1978

Ozone concentration		Measurement^{a,b} method	Exposure duration and activity^{c}	Observed effect(s)^{d}	No. and sex of subjects	Reference
$\mu g/m^3$	ppm					
980	0.5	CHEM, NBKI	2 hr R (9) & IE (37) for 30 min	Changes in pulmonary function (FVC, $FEV_{1.0}$, FEF_{25-75}) were greatest immediately following exercise. Heat stress potentiated the response while relative humidity had insignificant effects.	14 male (divided into 2 exposure groups)	Folinsbee et al., 1977b
980	0.5	MAST, NBKI	6 hr IE (44) for two 15-min periods	FVC, $FEV_{3.0}$, and SG_{aw} decreased and R_L increased. Nonsmokers were more susceptible. Inconsistent changes in lung mechanics and small airway function.	19 male 1 female (equally divided by smoking history)	Kerr et al., 1975
1176	0.6	CHEM, NBKI	2 hr (noseclips) R	Bronchoreactivity to histamine increased following exposure; persisted for up to 3 weeks; blocked by atropine.	3 male 5 female	Golden et al., 1978
1176	0.6	CHEM, NBKI	2 hr IE for two 15-min periods	Significant decrements in spirometric variables (19%-35%). Cough and pain on deep inspiration most frequently reported; no symptoms persisted beyond 48 hr.	20 male	Ketcham et al., 1977
1176 1568	0.6 0.8	MAST	2 hr R(9)	DL_{CO}: mean decrease of 25% (11/11 subjects). VC: mean decrease of 10% (10/10 subjects). $FEV_{0.75}$ x 40: mean decrease of 10%. FEF_{25-75}: mean decrease of 15%, which was not significant. Mixing efficiency: no change (2/2 subjects). Airway resistance: slight increase, but within normal limits. Dynamic compliance: no change (2/2 subjects). Substernal soreness and tracheal irritation 6 to 12 hr after exposure.	10 male 1 female	Young et al., 1964
1470	0.75	MAST, NBKI	2 hr IE (20-25) @ 15-min intervals	HR_{max}, $\dot{V}_E$, V_T, $\dot{V}O_{2max}$, and maximum workload all decreased. At maximum workload only, f_B increased (45%) and V_T decreased (29%).	13 male	Folinsbee et al., 1977a
1470	0.75	MAST, NBKI	2 hr R & IE (2XR) @ 15-min intervals	FEF_{50} and P_{ST}TLC decreased, R_L increased; returned to control levels within 24 hr. IE increased changes in R_L, C_{dyn}, $maxP_{tp}$, and spirometry. Cough and substernal soreness reported.	13 male: 10(R) & 3(IE)	Bates et al., 1972

TABLE 10-1 (continued). HUMAN EXPERIMENTAL EXPOSURE TO OZONE UP TO 1978

Ozone concentration		Measurement method[a,b]	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
μg/m³	ppm					
1764	0.9	MAST, NBKI	5 min CE	SG_{aw} decreased during and 5 min following exposure. Recovery complete within 30 min post-exposure.	4 male	Kagawa and Toyama, 1975
2940 3920	1.5- 2.0	I	2 hr R	VC: decreased 13% immediately after exposure; returned to normal in 22 hr. $FEV_{3.0}$: decreased 16.8% after 22 hr. Maximum breathing capacity decreased very slightly. CNS depression, lack of coordination, chest pain, tiredness for 2 weeks.	1 male	Griswold et al., 1957
1960 5880	1- 3	MAST	10-30 min R	VC: mean decrease of 16.5% (4/8 subjects showed decrease > 10%). $FEV_{1.0}$: mean decrease of 20% (5/8 subjects showed decrease > 10%. FEF_{25-75}: mean decrease of 10.5% (5/6 subjects showed a decrease). MBC: decrease of 12% (5/8 subjects showed decrease). DL_{CO}: decrease of 20 to 50% in 7/11 subjects; increase of 10 to 50% in 4/11 subjects; only 5/11 subjects tolerated 1 to 3 ppm for full 30 min. Wide variations in DL_{CO}. Headache, shortness of breath, lasting more than 1 hr.	11 subjects	Hallett, 1965
9800 19600	5- 10	I	Not available	Drowsiness and headache reported.	3 male	Jordan and Carlson, 1913

[a] Measurement methods: MAST = KI-coulometric (Mast meter); I = iodometric; CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry.

[b] Calibration methods: NBKI = neutral buffered potassium iodide.

[c] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or in multiples of resting ventilation.

[d] See Glossary for the definition of symbols.

Source: U.S. Environmental Protection Agency (1978).

have been provided to give the reader an overview of the studies discussed in the text and provide some additional information about measurement techniques and exposure protocols. Unless otherwise stated, the O_3 concentrations presented in the text and tables are the levels cited in the original manuscript. No attempt has been made to convert the concentrations to a common standard, although suggestions for conversion along with a discussion of O_3 measurement can be found in Chapter 4.

10.2 ACUTE PULMONARY EFFECTS OF OZONE

10.2.1 Introduction

The most prevalent and prominent pulmonary responses to O_3 exposure are cough, substernal pain upon deep inspiration, and decreased lung volumes (forced vital capacity, FVC; forced expiratory volume in 1s, $FEV_{1.0}$; tidal volume, V_T). Less substantial increases in airway resistance (R_{aw}) also occur. In most of the studies reported, greatest attention has been accorded decrements in $FEV_{1.0}$, as this variable represents a summation of changes in both volume and resistance. While this is true, it must be pointed out that for exposure concentrations critical to the standard-setting process (i.e., $\leq$0.3 ppm O_3), the observed decrements in $FEV_{1.0}$ primarily reflect FVC decrements of similar magnitude, with little or no contribution from changes in resistance. As examples, for subjects exposed to 0.3 ppm O_3 and performing exercise with associated minute ventilations ($\dot{V}_E$) of 31, 50, or 67 L/min, decrements in $FEV_{1.0}$ and FVC were 0.23 and 0.11, 0.31 and 0.29, 0.38 and 0.40 liters, respectively (Folinsbee et al., 1978). For subjects performing heavy exercise ($\dot{V}_E$ = 65 L/min) and exposed to 0.12, 0.18, 0.24, or 0.30 ppm O_3, decrements in $FEV_{1.0}$ and FVC were 0.21 and 0.17, 0.29 and 0.23, 0.59 and 0.53, 0.74 and 0.66 liters, respectively (McDonnell et al., 1983). In another study of subjects performing heavy exercise ($\dot{V}_E$ = 57 L/min and exposed to polluted ambient air (mean O_3 concentration = 0.15 ppm), 0.16 or 0.24 ppm O_3, decrements in $FEV_{1.0}$ and FVC were 0.20 and 0.18, 0.24 and 0.24, 0.74 and 0.73 liters, respectively (Avol et al., 1984). Thus, it is highly probable that most of the decrements in $FEV_{1.0}$ reported to result from O_3 exposure are indicative of restrictive changes and that little or no change in $FEV_{1.0}$/FVC occurs which would indicate resistive changes.

10.2.2 At-Rest Exposures

Results from studies reported prior to 1978 (Table 10-1) indicate that impairment of pulmonary function and pulmonary symptoms occur when normal subjects are exposed for 2 hr at rest to 1176-1568 $\mu g/m^3$ (0.6-0.8 ppm) of O_3 (Young et al., 1964), and to 1479 $\mu g/m^3$ (0.75 ppm) of O_3 (Bates et al., 1972; Silverman et al., 1976). In addition to decrements in the usual indicators of pulmonary function, Young et al. (1964) also found decreases in diffusion capacity of the lung (D_LCO).

Results from studies of at-rest exposures published since 1978 (Table 10-2) have generally confirmed these earlier findings. Folinsbee et al. (1978) observed decrements in FVC, $FEV_{1.0}$, and other spirometric variables when 10 normal subjects rested for 2 hr while exposed to 980 $\mu g/m^3$ (0.5 ppm) of O_3; R_{aw} was not affected. No changes in pulmonary function resulted from exposures to 588 or 196 $\mu g/m^3$ (0.3 or 0.1 ppm) of O_3. Horvath et al. (1979) reported that decreases in FVC and $FEV_{1.0}$ resulted from 2-hr at-rest exposures of 15 subjects (8 males, 7 females) to 980 and 1470 $\mu g/m^3$ (0.50 and 0.75 ppm) of O_3; the decreases at 0.75 ppm were greater than those at 0.50 ppm of O_3. No changes in pulmonary function were observed at 490 $\mu g/m^3$ (0.25 ppm) of O_3.

Kagawa and Tsuru (1979a) observed small decreases in specific airway conductance (SG_{aw}) when three subjects rested for 2 hr while exposed to 588 and 980 $\mu g/m^3$ (0.3 and 0.5 ppm) of O_3. In contrast to other studies, this is the only report of changes in airway resistance resulting from at rest exposures to O_3.

König et al. (1980) exposed 14 healthy nonsmokers (13 men, 1 woman) for 2 hr at rest to 0, 196, 627, and 1960 $\mu g/m^3$ (0.0, 0.10, 0.32, and 1.0 ppm) of O_3. Specific airway conductance was measured and samples of arterialized ear lobe capillary blood were taken for determinations of oxygen tension (PO_2) before and after the exposures. No changes in PO_2 or SG_{aw} were observed. Subjective symptoms (substernal burning) were reported by two individuals at 196 $\mu g/m^3$ (0.1 ppm), by three at 627 $\mu g/m^3$ (0.32 ppm), and by eight at 1960 $\mu g/m^3$ (1.0 ppm) of O_3.

10.2.3 Exposures With Exercise

The majority of controlled human studies since 1978 have been concerned with the effects of combined rest and exercise exposures to various concentrations of O_3 for variable periods of time (Table 10-2). Exercise during these

TABLE 10-2. STUDIES ON ACUTE PULMONARY EFFECTS OF OZONE SINCE 1978

Ozone concentration $\mu g/m^3$	Ozone concentration ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
157 314 470 627	0.08 0.16 0.24 0.32	UV, UV	1 hr CE (57)	Small decreases in FVC and $FEV_{1.0}$ at 0.16 ppm with larger decreases at ≥0.24 ppm; lower-respiratory symptoms increased at ≥0.16 ppm. Incomplete recovery of function and symptoms 1 hr postexposure.	42 male 8 female (competitive bicyclists)	Avol et al., 1984
196	0.1	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No effect on PaO_2 or R_{aw} taking into account intra-individual variation.	11 male	von Nieding et al., 1979
196 294 392 490	0.10 0.15 0.20 0.25	UV, UV	2 hr IE (68) (4) 14-min periods	Concentration-response curves produced; exponential decreases in FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, SG_{aw}, IC, and TLC with increasing O_3 concentration; at any given O_3 concentration, linear decreases in FVC and $FEV_{1.0}$ with time of exposure. Significant individual variation in response. Cough, nose and throat irritation, and chest discomfort or tightness also showed significant concentration-response relationships.	20 male	Kulle et al., 1985
196 588 980	0.1 0.3 0.5	CHEM, NBKI	2 hr R (10), IE (31, 50, 67) @ 15-min intervals	Changes in pulmonary function found at 0.5 ppm during R and 0.3 and 0.5 ppm with IE. The magnitude of spirometric changes was generally related to ozone concentration and minute ventilation, but concentration showed stronger association. Effective dose-functional response curves developed.	40 male (divided into 4 exposure groups)	Folinsbee et al., 1978
196 627 1960	0.1 0.32 1.0	MAST, NBKI	2 hr R	No changes in SR_{aw} or PO_2 following exposure; SR_{aw} increased with ACh challenge at ≥0.32 ppm; SR_{aw} increased in 2/3 COLD patients at 0.1 ppm.	13 male 1 female (3 COLD) (1 asthma)	König et al., 1980
235 353 470 588 784	0.12 0.18 0.24 0.30 0.40	CHEM, UV	2.5 hr IE (65) @ 15-min intervals	Small decreases in FVC, $FEV_{1.0}$, and $FEF_{25-75\%}$ at 0.12 and 0.18 ppm with larger decreases at ≥0.24 ppm; f and SR_{aw} increased and V_T decreased at ≥0.24 ppm; regression curves produced; coughing reported at all concentrations, pain and shortness of breath at ≥0.24 ppm.	135 male (divided into six exposure groups)	McDonnell et al., 1983
235 353 470 588 784	0.12 0.18 0.24 0.30 0.40	CHEM, UV	2.5 hr IE (65) @15-min intervals	Individual responses to O_3 (FVC, $FEV_{1.0}$) were highly reproducible for periods as long as 10 months and at O_3 concentrations ≥ 0.18 ppm; large intersubject variability in response due to intrinsic responsiveness to O_3.	32 male	McDonnell et al., 1985a

TABLE 10-2 (continued). STUDIES OF ACUTE PULMONARY EFFECTS OF OZONE SINCE 1978

Ozone concentration		Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
μg/m³	ppm					
235	0.12	CHEM, UV	2.5 hr IE (39) @ 15-min intervals	Small decrease in $FEV_{1.0}$; decrement persists for 24 hr. No change in frequency or severity of cough.	23 male (children aged 8-11 yr)	McDonnell et al., 1985b,c
235	0.12	UV	1 hr (mouthpiece) R	No significant changes in pulmonary function or subjective symptoms.	4 male 6 female (adolescents aged 13-18 yr)	Koenig et al., 1985
297 594	0.15 0.30	UV, UV	1 hr (mouthpiece) CE (55) + heat	Increased f_R, decreased V_T and $\dot{V}_A$ at 0.3 ppm; FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, and TLC decreased at 0.3 ppm. Most subjects reported pain on inspiration and coughing at 0.3 ppm. FVC decreased with increased temperature; interaction of O_3 with increased temperature for f_R and $\dot{V}_A$.	10 female	Gibbons and Adams, 1984
294 588	0.15 0.3	CHEM, NBKI	2 hr IE @ 15-min intervals	Small decreases in SG_{aw} and FVC after exposure to 0.15 and 0.30 ppm O_3. Increased ΔN_2 at 0.15 ppm O_3. Questionable statistics.	15 male	Kagawa, 1983a, 1984
392	0.2	UV, NBKI	2 hr IE (2xR) @ 15-min intervals	No meaningful changes in PAO_2, PaO_2, and $P(A-a)O_2$. Inconsistent changes in spirometric, plethysmographic, and ventilatory distribution variables.	13 male 5 female	Linn et al., 1979
392 588 784	0.2 0.3 0.4	UV, UV	30-80 min (mouthpiece) CE (34.9, 61.8)	Progressive impairment of lung function with increasing effective dose; questionable significance during CE (61.8).	8 male	Adams et al., 1981
392 686	0.20 0.35	UV, UV	1 hr (mouthpiece) IE (77.5) @ variable competitive intervals CE (77.5)	FVC, $FEV_{1.0}$, and FEF_{25-75} decreased, subjective symptoms increased with O_3 concentration; f_B increased and V_T decreased during CE; no effect on $\dot{V}O_2$, HR, $\dot{V}_E$, or $\dot{V}_A$. No exposure mode effect.	10 male (distance runners)	Adams and Schelegle, 1983

TABLE 10-2 (continued). STUDIES OF ACUTE PULMONARY EFFECTS OF OZONE SINCE 1978

Ozone concentration µg/m³	ppm	Measurement^{a,b} method	Exposure duration and activity^{c}	Observed effect(s)^{d}	No. and sex of subjects	Reference
392 823 980	0.2 0.42 0.50	UV, UV	2 hr IE (30 for male, 18 for female subjects) @ 15-min intervals	Pre-exposure to 0.2 ppm did not alter response to higher concentrations; $FEV_{1.0}$ decreased in sensitive subjects (n = 9) at 0.2 ppm; no significant sex differences.	8 male 13 female	Gliner et al., 1983
392 784	0.2 0.4	UV, NBKI	2 hr IE (2xR) @ 15-min intervals	SR_{aw} increased with histamine challenge in 4 subjects at 0.4 ppm. "Adaptation" shown with repeated exposures.	12 male 7 female (divided into three exposure groups)	Dimeo et al., 1981
412	0.21	UV, UV	1 hr CE (81)	Decreases in FVC (6.9%), $FEV_{1.0}$ (14.8%), $FEF_{25-75\%}$ (18%), IC (11%), and MVV (17%). Symptoms reported: laryngeal and tracheal irritation, soreness, and chest tightness on inspiration.	6 male 1 female (distance cyclists)	Folinsbee et al., 1984
490	0.25	UV, UV	1 hr CE (63)	FVC, FEV_1, $FEF_{25-75\%}$, $FEF_{75-85\%}$, MVV, and IC decreased; decrements in FEV_1, were 6% and 15% larger with reexposure 12 and 24 hr later, respectively. Increased responsiveness to O_3 persisted in some subjects for 48 hr but was lost within 72 hr. Symptoms paralleled the changes in lung function.	19 male 7 female (divided into four exposure groups)	Folinsbee and Horvath, 1986
490 980 1470	0.25 0.50 0.75	CHEM, NBKI	2 hr R (8)	Spirometry: FVC, $FEV_{1.0}$, and MMFR decreased immediately following 0.75 ppm; FVC and $FEV_{1.0}$ decreased immediately following 0.5 ppm. Metabolism: respiratory exchange ratio and ventilatory equivalent increased (0.75 ppm); oxygen uptake decreased at all O_3 concentrations. Increased $\dot{V}_E$ during exposure facilitates decrement in lung function but does not facilitate return to normal following exposure. No effect on max $\dot{V}O_2$ following exposure.	8 male 7 female	Horvath et al., 1979
588	0.3	UV, NBKI	1 hr (mouthpiece) CE @50% $\dot{V}O_{2max}$ +Vit E	RV increased while VC and $FEV_{1.0}$ decreased with O_3. Expired pentane (lipid peroxidation) increased with exercise but not O_3 exposure; attenuated by vitamin E supplementation.	5 male 5 female	Dillard et al., 1978

TABLE 10-2 (continued). STUDIES OF ACUTE PULMONARY EFFECTS OF OZONE SINCE 1978

Ozone concentration $\mu g/m^3$	Ozone concentration ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
588	0.3	MAST, BAKI	1 hr (mouthpiece) CE (34.7 for female and 51 for male subjects)	FVC, FEV$_{1.0}$ and FEF$_{25-75\%}$ decreased; f_B increased and V_T decreased with exercise; nonsmokers and females may be more sensitive; increase in subjective complaints noted.	12 male 12 female (equally divided by smoking history)	DeLucia et al., 1983
588 980	0.3 0.5	CHEM, NBKI	2 hr R	SG_{aw} decreased at 0.3 and 0.5 ppm. Tendency toward increased bronchial reactivity to ACh challenge. Smoking effects were similar to those of ozone.	6 male (equally divided by smoking history)	Kagawa and Tsuru, 1979a
725 1470	0.37 0.75	CHEM, NBKI	2 hr R	FEV$_{1.0}$ decreased at 0.37 ppm; FVC and $\dot{V}_{max50\%}$ decreased at 0.75 ppm.	26 male 6 female (habitual smokers)	Shephard et al., 1983
980 1470	0.50 0.75		2 hr IE (2.5xR) @ 15-min intervals	FVC, FEV$_{1.0}$, $\dot{V}_{max50\%}$, $\dot{V}_{max25\%}$ decreased. No interaction between cigarette smoking and O_3 but smokers may have decreased responsiveness to O_3.		
784	0.4	CHEM, NBKI	3 hr IE (4-5xR) for 15 min	FVC and FEV$_{1.0}$ decreased and bronchial reactivity to methacholine increased following exposure. Responses attenuated with repeated exposure.	13 male 11 female (divided into 2 phases)	Kulle et al., 1982b Kulle, 1983
784	0.4	CHEM, UV	2.5 hr IE (71) @ 15-min intervals	SR_{aw} increased and FVC, FEV$_1$, FEF$_{25-75\%}$, and TLC decreased with O_3; f_B increased and V_T decreased with exercise; no change in FRC or RV. Atropine pretreatment prevented the increased R_{aw} with O_3, partially blocked the decreases in forced expiratory flow, but did not prevent the O_3-induced decreases in FVC and TLC, change in exercise ventilation, or reported symptoms of cough and pain on deep inspiration.	8 male	Beckett et al., 1985

TABLE 10-2 (continued). STUDIES OF ACUTE PULMONARY EFFECTS OF OZONE SINCE 1978

Ozone concentration µg/m³	Ozone concentration ppm	Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
882	0.45	UV, UV	2 hr IE (27) @ 20-min intervals	FVC, FEV_1, FEV_3, and $FEF_{25-75\%}$ decreased; decrements were ~7% larger with reexposure 48 hr later. RV increased and TLC decreased after exposure; there were no significant changes in FRC or ERV.	1 male 5 female	Bedi et al., 1985
980	0.5	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals + Vit E	$FEV_{1.0}$ decreased in both placebo and vitamin E - supplemented subgroups; FVC decreased only in the placebo group. No significant effect of vitamin E.	9 male 25 female	Hackney et al., 1981
				No change in symptoms; FVC, $FEV_{1.0}$, $FEF_{25\%}$, $FEF_{50\%}$, ΔN_2, and TLC decreased in both placebo and vitamin E-supplemented subgroups. No significant effect of vitamin E.	22 male	
1176	0.6	UV, NBKI	2 hr (noseclip) IE (2xR) @ 15-min intervals	SR_{aw} increased in nonatopic subjects (n = 7) with histamine and methacholine and in atopic subjects (n = 9) with histamine following exposure, returning to control values by the following day; response prevented by pre-treatment with atropine aerosol.	11 male 5 female (divided by history of atopy)	Holtzman et al., 1979

[a] Measurement method: MAST = KI-coulometric (Mast meter); CHEM = gas phase chemiluminescence; UV = ultraviolet photometry.

[b] Calibration method: NBKI = neutral buffered potassium iodide; BAKI = boric acid potassium iodide; UV = ultraviolet photometry.

[c] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or as a multiple of resting ventilation.

[d] See Glossary for the definition of symbols.

exposures has been at different intensities and at different times during the exposures. The level of minute ventilation ($\dot{V}_E$), which varies with exercise intensity, is a primary determinant of the magnitude of pulmonary effects resulting from exposure to a given level of O_3. Therefore, results from studies using different regimens of exercise, even with exposure to the same O_3 concentration, may be difficult to compare. Most studies used alternating 15-min periods of rest and exercise. Pulmonary function and/or subjective symptoms were usually measured pre- and post-exposure. In a few studies, such measurements were also made during the rest periods after each exercise period. Exposures in these studies were usually performed only on one day, and were therefore likely to induce smaller functional decrements than would have been observed if subjects had been exposed on two sequential days, as noted in Section 10.3 entitled "Pulmonary Effects Following Repeated Exposure to Ozone."

Other factors that may influence the results obtained by different investigators and account for some of the inconsistencies observed among the findings from various studies are discussed in this chapter. Such factors include experimental design (more specifically: number of subjects, exposure time, recurrent exposures, length of and sequencing of exercise periods, and time of measurements), and specific measurement techniques used to determine O_3 concentration (see Chapter 4) and to characterize pulmonary responses. The variability of intrinsic responsiveness of individual subjects to O_3, effects of O_3 on subjects with pulmonary disease, and other factors affecting the responsiveness of subjects to O_3, such as smoking history, sex, and environmental conditions, are discussed in this section. Studies on the interaction between O_3 and other pollutants are presented in Section 10.5.

As previously stated, increased $\dot{V}_E$ accompanying exercise is one of the most important contributors to pulmonary decrements during O_3 exposure. While the more recent reports include actual measurements of $\dot{V}_E$ obtained during exposure, earlier publications often included only a description of the exercise regimen. Table 10-3 may aid the reader in estimating the $\dot{V}_E$ associated with a given exercise regimen.

The values for O_2 consumption and $\dot{V}_E$ in Table 10-3 are approximate estimates for average physically fit males exercising on a bicycle ergometer at 50 to 60 rpm (if rpms are higher or lower, values may be different). Note that individual variability is great and that the level of physical fitness, age, level of training, and other physiological factors may modify the estimated values. The only precise method of obtaining these data is to actually measure

TABLE 10-3. ESTIMATED VALUES OF OXYGEN CONSUMPTION AND MINUTE VENTILATION ASSOCIATED WITH REPRESENTATIVE TYPES OF EXERCISE[a]

Level of work	Work Performed watts	Work Performed kg-m/min[b]	O_2 consumption, L/min	Minute ventilation, L/min	Representative activities[c]
Light	25	150	0.65	12-16	Level walking at 2 mph; washing clothes
Light	50	300	0.96	17-23	Level walking at 3 mph; bowling; scrubbing floors
Moderate	75	450	1.25	23-30	Dancing; pushing wheelbarrow with 15-kg load; simple construction; stacking firewood
Moderate	100	600	1.54	29-38	Easy cycling; pushing wheelbarrow with 75-kg load; using sledgehammer
Moderate	125	750	1.83	35-46	Climbing stairs; playing tennis; digging with spade
Heavy	150	900	2.12	42-55	Cycling at 13 mph; walking on snow; digging trenches
Heavy	175	1050	2.47	52-67	Cross-country skiing; rock climbing; stair climbing with load; playing squash and handball; chopping with axe
Very Heavy	200	1200	2.83	62-79	
Very heavy	225	1350	3.19	73-93	
Very heavy	250	1500	3.55	89-110	Level running at 10 mph; competitive cycling
Severe	300	1800	4.27	107-132	Competitive long distance running; cross-country skiing

[a] See text for discussion.

[b] kg-m/min = work performed each minute to move a mass of 1 kg through a vertical distance of 1 m against the force of gravity.

[c] Adapted from Åstrand and Rodahl (1977).

the $\dot{V}_E$ and O_2 consumption. If exercise is conducted on a treadmill, adequate relative standards for O_2 consumption and $\dot{V}_E$ can not be estimated. Thus, with such activity, there is an absolute need to measure these variables.

Bates et al. (1972) and Bates and Hazucha (1973), as described in the previous O_3 criteria document (U.S. Environmental Protection Agency, 1978), were the first to consider the role of increased ventilation due to exercising in an O_3 environment. These observations emphasized an important aspect of ambient exposure; namely, that individuals who are engaged in some type of activity during ambient exposure to polluted air experience greater pulmonary function decrement than resting individuals.

Hazucha et al. (1973) reported data obtained on 12 subjects exposed for 2 hr to either 725 (n=6) or 1470 (n=6) μg/m^3 (0.37 or 0.75 ppm) of O_3. These subjects performed light exercise ($\dot{V}_E$ reported to be double resting ventilation) alternately every 15 minutes. Three subjects also had total lung capacity (TLC), residual volume (RV), and closing capacity (CC) measured before and after 2-hr exposure to 1470 μg/m^3 (0.75 ppm) of O_3. Significant decreases in lung function derived from the measurements of forced expiratory spirometry were observed at both 0.37 ppm ($P < 0.05$) and 0.75 ppm ($P < 0.001$) of O_3; the decrease was greater at the higher level of O_3. After exposures, all subjects complained to varying degrees of substernal soreness, chest tightness, and cough. While the number of subjects was small and the results therefore inconclusive, the mean RV and CC increased and TLC was unchanged after exposure to 0.75 ppm of O_3.

Kerr et al. (1975) reported small, but significant, decreases in FVC, $FEV_{3.0}$, R_L, and SG_{aw} when 20 subjects were exposed to 980 μg/m^3 (0.5 ppm) of O_3 for 6 hr with two 15-min periods of medium exercise (100 W). The symptoms of dry cough and chest discomfort were also experienced after exposure. No changes in TLC, FRC, C_{st}, dN_2, or D_LCO were observed.

Folinsbee et al. (1977b) demonstrated that the heightened pulmonary effect of O_3 associated with intermittent exercise during exposure occurred principally, if not entirely, during the exercise period. In this study, involving subjects who had exercised for a single 30-min period during a 2-hr 980-μg/m^3 (0.50-ppm) O_3 exposure, the maximum impairment of forced expiratory spirometry appeared immediately (2 to 4 min) after exercise (Figure 10-1). Despite continued exposure to O_3, but at rest, pulmonary function either improved or showed no further impairment. No change in RV or R_{aw} was observed, while TLC was reduced.

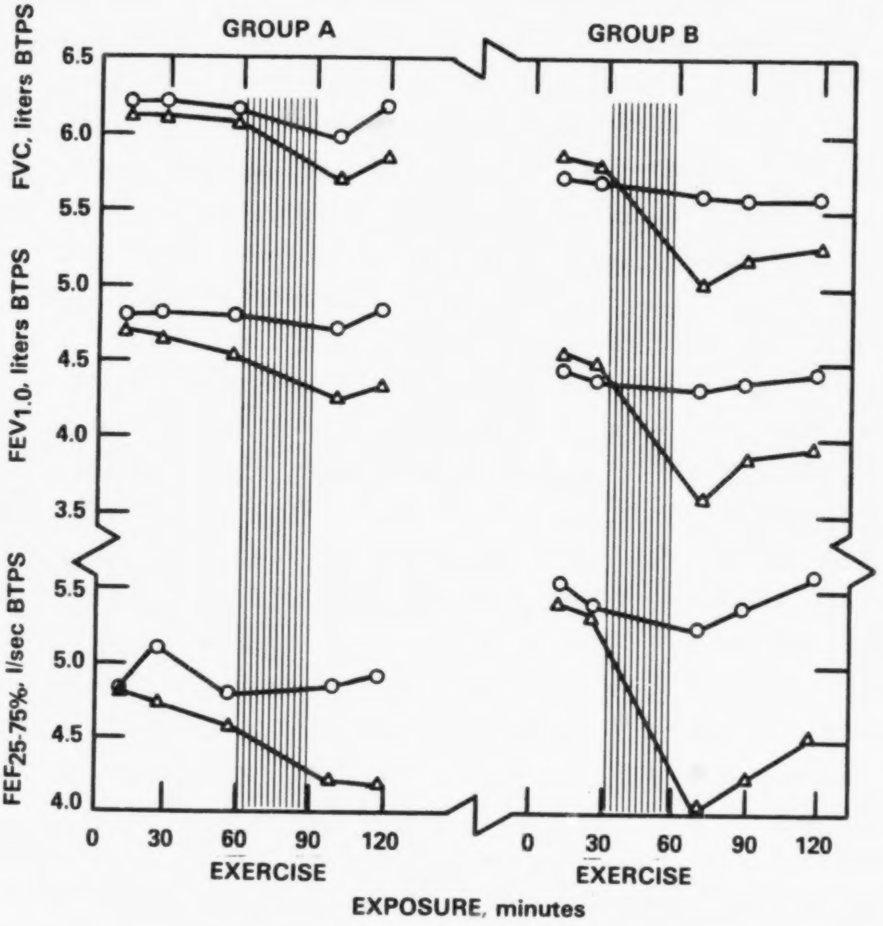

Figure 10-1. Change in forced vital capacity (FVC), forced expiratory volume in 1-sec ($FEV_{1.0}$), and maximal mid-expiratory flow ($FEF_{25-75\%}$) during exposure to filtered air (○) or ozone (△) (0.5 ppm) for 2 hr. Exercise at 45% maximal aerobic capacity (max $\dot{V}O_2$) was performed for 30 min by Group A after 60 min of ozone exposure and by Group B after 30 min of ozone exposure.

Source: Folinsbee et al. (1977b).

Folinsbee et al. (1978) reported results from 40 subjects in studies designed to evaluate the effects of various concentrations of O_3 at several different levels of activity from rest through heavy exercise. Half of the subjects had previously resided in an area having high O_3 concentrations; 14 reported symptoms associated with irritation or breathing difficulty on high-pollution days. Five subjects who had not resided in such areas reported similar symptoms upon visiting a high-oxidant-pollution region. Nine subjects had a history of allergy, 11 were former smokers, and one had had asthma as a child. Ten subjects in each of four groups were exposed four times, in random order, to filtered air or 196, 588, or 980 $\mu g/m^3$ (0, 0.10, 0.30, or 0.50 ppm) of O_3. One group rested throughout the exposure. The other three groups exercised at four intervals throughout the exposure; each 15-min exercise period was followed by a 15-min rest period. Each subject in the three exercise groups walked on a treadmill at a level of activity to produce minute ventilations of approximately 30, 50, or 70 L/min, respectively. The integrated minute ventilatory volumes for the total 2 hr of exposure were 10, 20.35, 29.8, and 38.65 L, respectively. No pulmonary changes were observed with exposure to filtered air or 196 $\mu g/m^3$ (0.10 ppm) of O_3 at any workload. At rest (10 L/min), pulmonary function changes were confined to 980 $\mu g/m^3$ (0.50 ppm) O_3 exposures. Some changes were apparent at the lowest work load (30 L/min) and 588 $\mu g/m^3$ (0.30 ppm) of O_3, and effects were more marked at 980 $\mu g/m^3$ (0.50 ppm) of O_3. At the two highest work loads (49 and 67 L/min), pulmonary function changes occurred at both 588 and 980 $\mu g/m^3$ (0.30 and 0.50 ppm), with the changes at 980 $\mu g/m^3$ (0.50 ppm) of O_3 usually significantly greater than those at 588 $\mu g/m^3$ (0.30 ppm) of O_3. During exercise, respiratory frequency was greater and tidal volume lower with O_3 exposure than with sham exposure. The change in respiratory pattern was progressive and was most striking at the two heaviest work loads and at the highest O_3 concentrations. Reductions in TLC and inspiratory capacity (IC), but not RV or functional residual capacity (FRC), were also noted.

Von Nieding et al. (1977) exposed normal subjects to 196 $\mu g/m^3$ (0.1 ppm) O_3 for 2 hr with light intermittent exercise and found no changes in either forced expiratory functions or symptoms. However, they found significant increases (~7 mm Hg) in both alveolar-arterial PO_2 difference and airway resistance (~0.5 cm $H_2O/L/s$) and a significant decrease in P_aO_2 (~7 mm Hg). These data were later reanalyzed (von Nieding et al., 1979) using more stringent statistical criteria and the changes in both airway resistance and PaO_2 were found to be nonsignificant. In both analyses, the nonparametric Wilcoxen procedure which ranks paired differences was used. In the 1977 analysis, PaO_2 and airway resistance changes ≤ 5 mm Hg and 0.5 cm $H_2O/L/s$, respectively, were considered as zero but used in the analysis. In the 1979 analysis, PaO_2 and airway resistance changes ≤ 5 mm Hg and 0.5 cm $H_2O/L/s$, respectively, and within the range of normal variation for each individual subject were not included in the analysis. Thus, data from about half the subjects analyzed in 1977 were included in the 1979 analysis.

In a study similar to that of von Nieding et al. (1977; 1979), Linn et al. (1979) exposed normal subjects to 392 $\mu g/m^3$ (0.2 ppm) of O_3. The 18 subjects exercised at twice resting ventilation for 15 min of every half hour. Blood and alveolar gas samples were taken shortly after 1 and 2 hr of their 2.5 hr of exposure. Blood samples were taken both from an arterialized ear lobe and a brachial artery. No significant differences between air and O_3 exposures were observed for changes in P_AO_2, P_aO_2 or $P_{(A-a)}O_2$.

Adams et al. (1981) required eight subjects (22 to 46 years of age) to exercise continuously (i.e., no rest periods) while orally inhaling 0.0, 392, 588, and 784 $\mu g/m^3$ (0.0, 0.2, 0.3, and 0.4 ppm) of O_3. The duration of the exercise periods varied from 30 to 80 min, and the two exercise loads were sufficient to induce minute ventilations of 34.9 and 61.8 L/min, respectively. Pulmonary functions were measured before and within 15 min after exercise. At both minute ventilations, decrements in forced expiratory spirometry were observed for exposures to 588 and 784 $\mu g/m^3$ (0.30 and 0.40 ppm) of O_3 with the magnitude of decrement greater at the higher minute ventilation. The magnitude of decrement also increased with increasing exposure time. No pulmonary effects were observed for exposures to clean air or 392 $\mu g/m^3$ (0.2 ppm) of O_3. The authors suggested that the detectable level for O_3 functional effects in healthy subjects during sustained exercise at a moderately heavy work load ($\dot{V}_E$ of ~62 L/min) occurred between O_3 concentrations of 392 and 588 $\mu g/m^3$ (0.2 and 0.3 ppm). The responses to continuous exercise were similar to those observed in studies using intermittent but equivalent exercise.

Kagawa (1983a; 1984) presented data on 15 subjects exercising intermittently (15 min exercise, 15 min rest) during a 2-hr exposure to 294 or 588 $\mu g/m^3$ (0.15 or 0.30 ppm) of O_3. These subjects reported the typical symptoms at the higher O_3 concentrations. Paired t-tests were used to compare responses to filtered air and O_3. SG_{aw} decreased 6.4 percent ($P < 0.05$) following the 294-$\mu g/m^3$ (0.15-ppm) exposure and 16.7 percent ($P < 0.01$) following the 588-$\mu g/m^3$

(0.30-ppm) exposure. In the latter environment, only FVC showed a significant ($P < 0.05$) decrement; FEV_1 was unaffected. These subjects had resided in a low-oxidant-pollutant environment.

McDonnell et al. (1983) provided further information related to high levels of ventilation during exercise in 135 healthy subjects exposed to O_3. Subjects were excluded from the study if they had smoked within 3 yr or had a history of asthma, allergy, rhinitis, cardiac disease, chronic respiratory disease, recent acute respiratory illness, or extensive exposure to pollutants. They divided their subjects into six groups, each group exposed to a different concentration of O_3; viz. 0.0 (n=20), 0.12 (n=22), 0.18 (n=20), 0.24 (n=21), 0.30 (n=21), and 0.40 (n=29) ppm, equivalent to 0.0, 235, 353, 470, 588, and 784 $\mu g/m^3$ of O_3. The subjects were exposed for 2.5 hr, with exposure consisting of alternating 15-min periods of rest and exercise ($\dot{V}_E$/BSA of $\cong$ 35 L/m^2 or $\dot{V}_E$ = 64 to 68 L/min) during the first 120 min. Forced expiratory spirometry and pulmonary symptoms were measured between 5 and 10 min after the final exercise (i.e., at 125 min of exposure), while plethysmography was performed between 25 and 30 min after the final exercise (i.e., at 145 min of exposure). The pulmonary symptom, cough, showed the greatest sensitivity to O_3 (it occurred at the lowest concentration, 235 $\mu g/m^3$ or 0.12 ppm of O_3). Small changes in forced expiratory spirometric measures (FVC, FEV_1, maximal mid-expiratory flow [$FEF_{25-75\%}$]) were suggested at 235 $\mu g/m^3$ (0.12 ppm) of O_3 and were definitely present at 353 $\mu g/m^3$ (0.18 ppm) of O_3. Greater changes were found at and above 470 $\mu g/m^3$ (0.24 ppm) of O_3. Significant decreases in tidal volume (V_T) and increases in respiratory frequency (f_R) during exercise (similar changes had been reported by other investigators) and specific airway resistance (SR_{aw}), pain on deep inspiration, and shortness of breath occurred at O_3 levels of >470 $\mu g/m^3$ (0.24 ppm). The sigmoid-shaped dose-response curves indicated a relatively large decrease in FVC, FEV_1, and $FEF_{25-75\%}$ between 353 and 470 $\mu g/m^3$ (0.18 and 0.24 ppm) O_3. However, in contrast to the results of other investigations, a plateau in response was suggested at the higher levels (>470 $\mu g/m^3$; 0.24 ppm) of O_3. Regarding SR_{aw}, a significant increase was observed beginning at 470 $\mu g/m^3$ (0.24 ppm) of O_3 and the magnitude of this change was greater with increasing O_3 levels. These findings are in agreement with the results of other investigators. The two different patterns in response plus the observation that individual changes in SR_{aw} and FVC were poorly correlated prompted these investigators to suggest that more than a single mechanism might have to be implicated to define the effects of O_3 on pulmonary functions. Findings from this study are particularly relevant in that a large subject population was studied and pulmonary effects were suggested at an O_3 concentration (235 $\mu g/m^3$; 0.12 ppm) lower than that for which they had previously been observed.

More recent studies on well-trained subjects have become available. Six well-trained men and one well-trained woman (all of the subjects except one male being a competitive distance cyclist) exercised continuously on a bicycle ergometer for 1 hr while breathing filtered air or 412 $\mu g/m^3$ (0.21 ppm) of O_3 (Folinsbee et al., 1984). They worked at 75 percent maximal aerobic capacity (max $\dot{V}_{O2}$) with mean minute ventilations of 89 L/min. Pulmonary function measurements were made pre- and post-exposure. Decreases occurred in FVC (6.9 percent), $FEV_{1.0}$ (14.8 percent), $FEF_{25-75\%}$ (18 percent), IC (11 percent), and maximum voluntary ventilation (MVV) (17 percent). The magnitude of these changes were of the same order as those observed in subjects performing moderate intermittent exercise for 2 hr in a 686-$\mu g/m^3$ (0.35-ppm) O_3 environment. Symptoms included laryngeal and/or tracheal irritation and soreness as well as chest tightness upon taking a deep breath.

Adams and Schelegle (1983) exposed 10 well-trained distance runners to 0.0, 392, and 686 $\mu g/m^3$ (0.0, 0.20, and 0.35 ppm) of O_3 while the runners exercised on a bicycle ergometer at work loads simulating either a 1-hr steady-state training bout or a 30-min warmup followed immediately by a 30-min competitive bout. These exercise levels were of sufficient magnitude (68 percent of their max $\dot{V}_{O2}$) to increase mean $\dot{V}_E$ to 77.5 L/min. In the last 30 min of the competitive exercise bout, minute ventilations were approximately 105 L/min. Subjective symptoms, including shortness of breath, cough, and raspy throat increased as a function of O_3 concentration for both continuous and competitive levels. The high ventilation volumes (77.5 L/min) resulted in marked pulmonary function impairment and altered ventilatory patterns (increased f_R and decreased V_T) when exercise was performed in 392 $\mu g/m^3$ (0.20 ppm) of O_3. Two-way analysis of variance (ANOVA) procedures performed on the pulmonary function data indicated significant decrements ($P < 0.0002$) for FVC, FEV_1, and $FEF_{25-75\%}$. The investigators noted that the decrements in $FEV_{1.0}$ were similar to those observed by Folinsbee et al. (1978) when the two studies were compared on the basis of effective dose. The concept of effective dose will be treated in a later section.

Avol et al. (1984; 1985) randomly exposed trained cyclists (n = 50) to 0, 157, 314, 470, and 627 $\mu g/m^3$ (0.0, 0.08, 0.16, 0.24, and 0.32) ppm O_3. Each exposure consisted of 10 min warm-up, 60 min of exercise at 50% max $\dot{V}O_2$ ($\dot{V}_E$ = 57 L/min), 5 min cool down (all performed on a bicycle ergometer), and 5 min post-exercise pulmonary function testing. Most subjects resided in the Los Angeles area and therefore were subject to prior exposure to ambient O_3. Two subjects had histories of asthma; all others were free of chronic respiratory disease. Three subjects were current smokers, while six others had previously smoked. Forced expiratory spirometry and respiratory symptoms were evaluated before exposure, immediately after exercise, and 1 hr after exposure. When compared to exposure at 0.0 ppm, significant decreases in FVC and $FEV_{1.0}$ and an increase in lower respiratory symptom score combined (cough, sputum, dyspnea, wheeze, substernal irritation, chest tightness) were observed following exposure at and above 314 $\mu g/m^3$ (0.16 ppm) O_3; no significant changes occurred with exposure to 157 $\mu g/m^3$ (0.08 ppm) O_3. An increasing number of subjects could not complete the 1 hr of exercise at O_3 concentrations of 470 and 627 $\mu g/m^3$ (0.24 and 0.32 ppm) without reducing their workloads. The magnitudes of change in FVC, FEV_1, and symptom score were concentration-dependent and remarkably consistent with those previously reported by McDonnell et al. (1983) (see Section 10.2.1). While they did not return to levels observed prior to exposure, substantial recovery of both function and symptoms was observed 1 hr following exposure. Significant changes in FVC, FEV_1, and lower respiratory symptom score also resulted from exposure to polluted ambient air with a mean O_3 concentration of 294 $\mu g/m^3$ (0.15 ppm) (see Section 11.2.1). Although the pulmonary changes in response to polluted ambient air appeared to be of lesser magnitude than those in reponses to the nearest generated O_3 level (314 $\mu g/m^3$; 0.16 ppm), the difference between the two exposures was not statistically significant.

Kulle et al. (1985) randomly exposed male nonsmokers (n = 20), with no history of chronic respiratory or cardiovascular disease, to 0, 196, 294, 392, and 490 $\mu g/m^3$ (0.0, 0.10, 0.15, 0.20, and 0.25 ppm) O_3 for 2 hr. Each exposure consisted of four cycles of 14 min treadmill exercise ($\dot{V}_E$ = 68 L/min) alternated with 16 min of rest. Forced expiratory spirometry was performed before exposure and 9 min after each exercise. Measurements of R_{aw} and V_{ts} (FRC) were made prior to and after each exposure; respiratory symptoms were evaluated after each exposure. Significant concentration-dependent decreases in FVC, $FEV_{1.0}$, FEF_{25-75}, SG_{aw}, IC, and TLC and increases in respiratory symptoms (cough, nose/throat irritation, chest discomfort) were observed; RV and FRC did not change with exposure to any concentration. Significant responses were best modeled as an exponential function of O_3 concentration. Additionally, FVC and $FEV_{1.0}$ decreased as a linear function of time of exposure. While these results are discussed by the authors as though significant changes resulted from exposure to 294 $\mu g/m^3$ (0.15 ppm) O_3, the magnitude of change at this concentration was quite small (<1 percent) when compared to preexposure levels. Moreover, while the statistical procedures (ANOVA) used by these investigators did indicate a significant O_3 effect when data from exposures to all O_3 concentrations were analyzed, no statistical comparisons of responses at individual O_3 concentrations were performed. Thus, the legitimacy of ascribing O_3 effects at any individual O_3 concentration is questionable and discussion of data should be confined to the overall concentration-response relationship.

10.2.4 Intersubject Variability and Reproducibility of Responses

In the majority of the above studies, assessment of the significance of results was typically based on the mean ± variance of changes in lung function resulting from exposure to O_3 as compared to exposure to clean air. Although consideration of mean changes is useful for making statistical inferences about homogeneous populations, it may not be adequate to describe the differences in responsiveness to O_3 among individuals. While the significant mean changes observed demonstrate that the differences in response between O_3 and clean air exposures were not due to chance, the variance of responses was quite large in most studies. While characterization of reports of individual responses to O_3 is useful since it permits an assessment of the proportion of the population that may actually be affected during O_3 exposure, statistical treatment of these data is still rudimentary and their validity is open to question.

Results from a small number of studies (Horvath et al., 1981; Gliner et al., 1983; McDonnell et al., 1983; Kulle et al., 1985) that have reported individual responses indicate that a considerable amount of intersubject variability does exist in the magnitude of response to O_3. Figure 10-2 illustrates the variability of responses in $FEV_{1.0}$ and SR_{aw} obtained from subjects exposed to different O_3 concentrations.

Decreases in $FEV_{1.0}$ ranging from 2 to 48 percent (mean = 18 percent) were reported by Horvath et al. (1981) for 24 subjects exposed for 2 hours to 823 $\mu g/m^3$ (0.42 ppm) of O_3 while performing moderate intermittent exercise. When

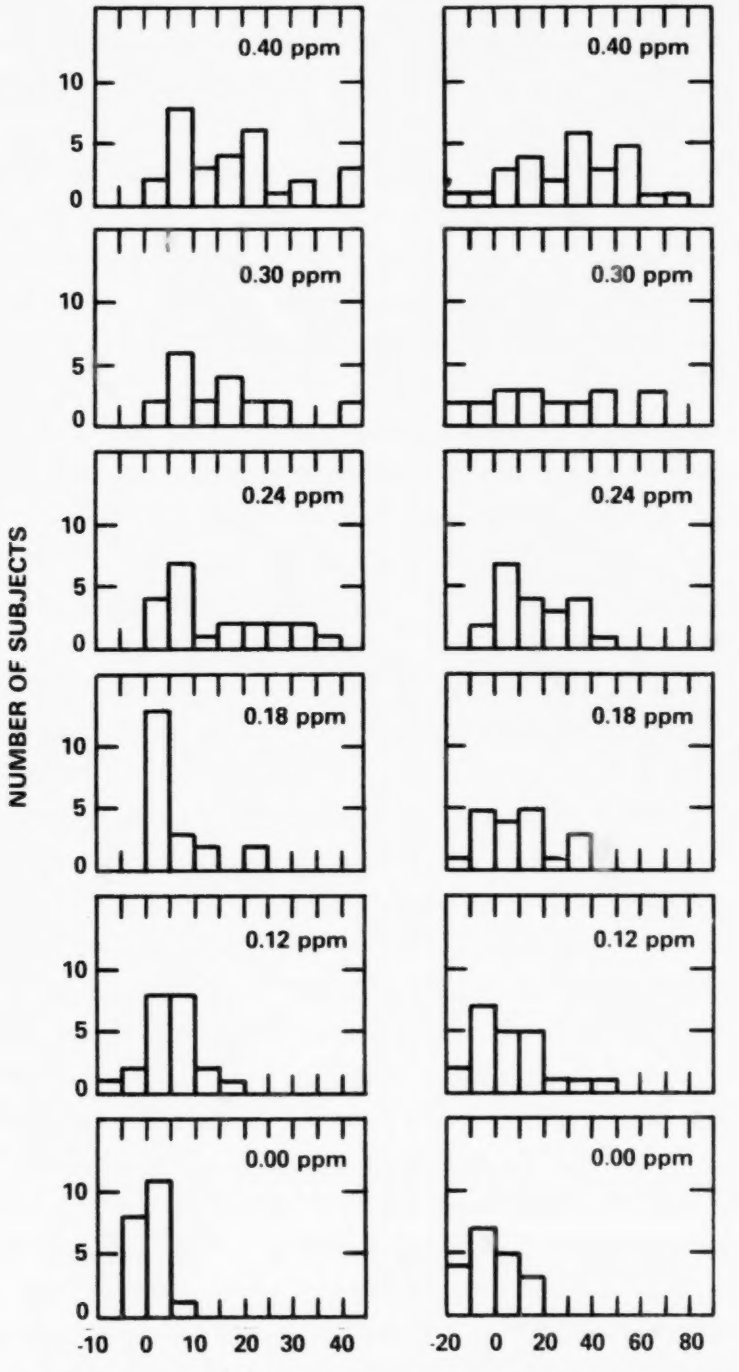

Figure 10-2. Frequency distributions of response (percent change from baseline) in specific airway resistance (SR_{aw}) and forced expiratory volume in 1-sec ($FEV_{1.0}$) for individuals exposed to six levels of ozone. One individual with 260% increase in SR_{aw} exposed to 0.4 ppm of ozone is not graphed.

Source: McDonnell et al. (1983).

these same subjects were exposed to clean air under the same conditions, the response of $FEV_{1.0}$ ranged from an 8-percent increase to an 11-percent decrease (mean = 0 percent).

Gliner et al. (1983) exposed subjects (13 females, 8 males) performing intermittent light exercise for 2 hr to clean air and 392 $\mu g/m^3$ (0.20 ppm) of O_3. Changes in $FEV_{1.0}$ resulting from clean-air exposure ranged between +7.8 percent and -7.5 percent (mean = 0 percent), while the range of changes in $FEV_{1.0}$ was +6.0 to -16.6 percent (mean = -3 percent) with exposure to 392 $\mu g/m^3$ (0.20 ppm) of O_3.

For subjects performing 2 hr of intermittent heavy exercise while exposed to O_3, McDonnell et al. (1983) observed changes in $FEV_{1.0}$ ranging from -1 to -45 percent (mean = -18 percent) at 784 $\mu g/m^3$ (0.40 ppm), -1 to -42 percent (mean = -17 percent) at 588 $\mu g/m^3$ (0.30 ppm), -1 to -36 percent (mean = -15 percent) at 470 $\mu g/m^3$ (0.24 ppm), 0 to -23 percent (mean = -6 percent) at 353 $\mu g/m^3$ (0.18 ppm), +7 to -16 percent (mean = -4 percent) at 235 $\mu g/m^3$ (0.12 ppm), and +2 to -6 percent (mean = -1 percent) in clean air. Large intersubject variability was also reported for changes in SR_{aw} during these exposures (Figure 10-2).

Kulle et al. (1985) exposed each of their 20 subjects to four O_3 concentrations for 2 hr with heavy intermittent exercise. For these subjects, changes in $FEV_{1.0}$ ranged from +5 to -2 (mean = +1 percent) in clean air, +10 to -4 percent (mean = +1 percent) at 196 $\mu g/m^3$ (0.10 ppm), +3 to -9 percent (mean = -1 percent) at 294 $\mu g/m^3$ (0.15 ppm), +3 to -16 percent (mean = -3 percent) at 392 $\mu g/m^3$ (0.20 ppm), and +1 to -36 percent (mean = -6 percent) at 490 $\mu g/m^3$ (0.25 ppm). Concentration-response curves were also constructed for individual subjects and individual O_3 responsiveness assessed. Three subjects exhibited a slight increase in FEV_1 following exposures to all four of the O_3 concentrations. Most of the remaining subjects demonstrated progressive decreases in $FEV_{1.0}$ with increasing O_3 concentrations. Five subjects exhibited $FEV_{1.0}$ decreases of <5 percent, seven subjects were between 5 and 10 percent, three subjects were between 10 and 15 percent, and two subjects exhibited $FEV_{1.0}$ decrease of >15 percent. The reported symptom of cough correlated with the observed decrements in FVC and FEV_1 ($r = 0.52$) and nose and throat irritation correlated with FEV_1 changes ($r = 0.49$).

The degree to which a subject's response to a given O_3 concentration can be reproduced is an indication of how precisely the measured response estimates that subject's intrinsic responsiveness. In a 1983 study, Gliner et al. exposed subjects performing intermittent light exercise for 2 hr to 392 $\mu g/m^3$ (0.20 ppm) of O_3 on three consecutive days, followed the next day by an exposure to either 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) of O_3. Each subject had also been exposed prior to or was exposed after the study to 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) O_3. For individual responses of $FEV_{1.0}$, a moderate correlation ($r = 0.58$) between changes resulting from the first exposure to 392 $\mu g/m^3$ (0.20 ppm) of O_3 and the second exposure to 823 or 980 $\mu g/m^3$ (0.42 or 0.50 ppm) of O_3 was observed. When responses in $FEV_{1.0}$ from the first and second exposures to 0.42 or 0.50 ppm O_3 were compared, the correlation between the two exposures was quite high ($r = 0.92$). Although these comparisons were confounded by possible effects of prior O_3 exposure, they do suggest that individual changes in $FEV_{1.0}$ resulting from O_3 exposure are reasonably reproducible. Moreover, a given individual's response to a single O_3 exposure is probably a reliable estimate of that individual's intrinsic responsiveness to O_3.

McDonnell et al. (1985a) exposed each of 32 subjects for 2 hr to one of five different O_3 concentrations (235, 353, 470, 588, and 784 $\mu g/m^3$; 0.12, 0.18, 0.24, 0.30, and 0.40 ppm) with intermittent heavy exercise. Each subject was exposed at least twice to the same O_3 concentration at 3 to 75-week intervals. The correlation coefficients between the two exposures closest in time (mean ± S.D. = 9 ± 4 weeks) for individual changes in FVC, $FEV_{1.0}$, and $FEF_{25-75\%}$ were 0.89, 0.91, and 0.83, respectively. Correlation coefficients were moderate for changes in SR_{aw} ($r = 0.63$) and the pulmonary symptoms of cough ($r = 0.75$), shortness of breath ($r = 0.65$), and pain upon deep respiration ($r = 0.48$). With a longer time between exposures (mean ± S.D. = 33 ± 20 weeks), changes in FVC ($r = 0.72$), $FEV_{1.0}$ ($r = 0.80$), and $FEF_{25-75\%}$ ($r = 0.76$) were nearly as reproducible. This high degree of reproducibility indicates that the magnitude of response to a single exposure is a reliable estimate of that subject's intrinsic responsiveness to O_3. Moreover, intersubject variability in magnitude of O_3-induced effects is probably the result of large differences in intrinsic responsiveness to O_3.

10.2.5 Prediction of Acute Pulmonary Effects

Nomograms for predicting changes in lung function resulting from the performance of light intermittent exercise while exposed to different O_3 concentrations were included in one of the earliest reports of the effects of

O_3 on normal subjects (Bates and Hazucha, 1973). Then in 1976, Silverman et al. reported that pulmonary function decrements were related as linear and second-order polynomial functions of the effective dose of O_3, defined as the product of concentration, exposure duration, and $\dot{V}_E$. Equations were derived from lung function measurements at 1 and 2 hr of exposure to 725, 980, and 1470 $\mu g/m^3$ (0.37, 0.50, and 0.75 ppm) of O_3 under conditions of both rest and intermittent exercise sufficient to increase $\dot{V}_E$ by a factor of 2.5. Although the fit of their data to linear and second-order curves was good, the authors also commented that for a given effective dose, exposure to a high concentration of O_3 for a short period of time induced greater functional decrements than a longer exposure to a lower concentration. This phenomenon implies that O_3 concentration is a more important contributor to response than is exposure duration. Moreover, they also observed extensive individual variability in pulmonary function changes, suggesting that use of effective dose is not satisfactory for predicting individual responses to O_3 exposure.

Since the inception of the concept of an effective dose, additional studies have used, and in some cases refined it for prediction of pulmonary responses to O_3 exposure. However, these prediction models must be interpreted with extreme caution since the data base is limited and the great intersubject variability in responsiveness to O_3 makes truly refined modeling of effective dose highly improbable. Extension of the effective-dose concept was accomplished in the studies of Folinsbee et al. (1978) on subjects at rest and performing intermittent exercise during 2-hr exposures to 0, 196, 588, and 980 $\mu g/m^3$ (0.0, 0.10, 0.30, and 0.50 ppm) of O_3. The exercise loads required $\dot{V}_E$ of some three, five, and seven times greater than resting ventilations. Again, the effective dose was calculated as the product of O_3 concentration x $\dot{V}_E$ (L/min) during exposure (includes both exercise and rest minute ventilation) x duration of exposure. Polynomial regression analyses were performed first on mean data at each level of $\dot{V}_E$, and second on all subject groups together after computing the effective dose. Predictions of pulmonary function changes in FEV_1 based on effective doses up to 1.5 ml O_3 agreed with data collected by other investigators. Prediction equations using the effective dose for all measured pulmonary functions were constructed. All equations were significant at the 0.01 level. These investigators also used a multiple regression approach to refine further the prediction of changes in pulmonary function resulting from O_3 exposure. Duration of exposure was not analyzed as a contributing factor since all exposures were of equal time. Their analyses indicate that essentially all of the variance of pulmonary responses could be explained by O_3 concentration and $\dot{V}_E$. For example, these two predictors accounted for approximately 80 percent (multiple r = 0.89) of the variance in $FEV_{1.0}$. Moreover, O_3 concentration accounted for more of variance than did $\dot{V}_E$, and for a given effective dose, exposure to a high concentration with a low $\dot{V}_E$ induced greater functional decrements than exposure to a lower concentration with elevated $\dot{V}_E$. Equations (with appropriately weighted O_3 concentration and $\dot{V}_E$) for predicting the magnitude of pulmonary decrements were also provided.

Adams et al. (1981) further extended the effective-dose concept in studies using a multiple regression approach and arrived at essentially the same conclusions reached by Folinsbee et al. (1978), namely that most of the variance for pulmonary function variables could be accounted for by O_3 concentration, followed by $\dot{V}_E$, and then by exposure time. Adams et al. emphasized the predominant importance of O_3 concentration and suggested that the detectable level for O_3 functional effects in healthy subjects during sustained exercise at a moderately heavy work load ($\dot{V}_E \sim 62$ L) occurred between O_3 concentrations of 392 and 588 $\mu g/m^3$ (0.2 and 0.3 ppm). The responses to continuous exercise were similar to those observed in studies using intermittent but equivalent exercise. They also noted, as had others, that the effective-dose concept was not satisfactory for predicting individual responses.

Colucci (1983) assembled data available from the literature and analyzed them with the purpose of constructing dose/effects profiles for predicting pulmonary responses to O_3 based on results combined from many different laboratories. Basically, he examined changes in R_{aw} and $FEV_{1.0}$ as functions of exposure rate (O_3 concentration x $\dot{V}_E$) and total exposure dose (exposure rate x duration of exposure), which is equivalent to effective dose. The correlation for changes in R_{aw} was slightly better than that for changes in $FEV_{1.0}$. The author states that he elected to use linear equations to fit the data rather than polynomials because he found little difference in the degree of correlation between the two methods. The analysis also found an attenuation in the rate of increase of SR_{aw} as $\dot{V}_E$ increased to higher levels; there was no attenuation of the decrease in $FEV_{1.0}$ as a function of increasing $\dot{V}_E$. This observation suggested to Colucci that different mechanisms may be involved in the effects on R_{aw} and $FEV_{1.0}$. Whether expressed as functions of exposure rate or total exposure dose, the patterns of pulmonary responses were approximately equivalent. This is not surprising since both Folinsbee et al. (1978) and Adams et al. (1981) had previously shown that most of the variance in pulmonary response depended primarily on O_3 concentration and $\dot{V}_E$. The overall finding, that increases in R_{aw} and decreases in $FEV_{1.0}$ are reasonably correlated with increases in effective dose of O_3, only confirms the results reported by previous investigators. As proposed by Folinsbee et al. (1978) and Adams et al. (1981), a better fit of the data may have been obtained had Colucci used multiple regression and equations that appropriately weighted the relative contributions of each of the exposure variables to pulmonary decrements.

10.2.6 Bronchial Reactivity

In addition to overt changes in pulmonary function, several studies have reported increased nonspecific airway sensitivity resulting from O_3 exposure. Airway responsiveness to the drugs acetylcholine (ACh), methacholine, or histamine is most often used to define nonspecific airway sensitivity.

Eight healthy nonsmoking men served as subjects (Golden et al., 1978) for evaluation of bronchial reactivity due to histamine after a 2-hr exposure to 1176 $\mu g/m^3$ (0.6 ppm) of O_3. The resting subjects breathed orally (a nose-clip was worn). These investigators concluded that O_3 exposure at this concentration and dose produced an enhanced response to histamine, which returned to normal within 1 to 3 weeks after exposure.

Kagawa and Tsuru (1979a) studied both smokers and nonsmokers exposed to 0.0, 588, and 980 $\mu g/m^3$ (0.0, 0.3, and 0.5 ppm) O_3. Their three nonsmoking subjects were exposed for 2 hr followed by measurements of bronchial reactivity to ACh. They found that these subjects demonstrated an increased reactivity to ACh. However, because of the small number of subjects and the large variability of responses, the results may not represent a significant effect.

The bronchial reactivity of atopic and nonatopic subjects was evaluated by Holtzman et al. (1979). They studied 16 healthy nonsmoking subjects and found that nine could be classified as "atopic" based on medical history and allergen skin testing. All subjects had normal pulmonary functions determined in preliminary screening tests and were asymptomatic. Both atopic and nonatopic subjects performed intermittent exercise while wearing noseclips and exposed by mouthpiece to filtered air and 1176 $\mu g/m^3$ (0.6 ppm) of O_3. Bronchial reactivity was determined 1 hr after exposure to each condition (when post-exposure SR_{aw} had returned to normal) by measuring the increase in SR_{aw} produced by inhalation of histamine or methacholine aerosols. In both atopic and nonatopic subjects, the bronchial response to histamine and methacholine was enhanced after O_3 exposure when compared to exposure in filtered air. The increase in SR_{aw} resulted predominantly from an increase in airway resistance, with only small changes in trapped gas volume. Symptoms of bronchial irritation were increased; however, these changes were transient, and were not detectable by the next day. This result contrasts with previous results observed by these investigators (Golden et al., 1978), which indicated that enhanced bronchial responsiveness persisted for a more prolonged period. Premedication with atropine sulfate aerosol prevented the increase in SR_{aw} after histamine inhalation. Atopic subjects appeared to respond to a greater degree than nonatopic subjects, although the pattern of change and the induction and time course of increased bronchial reactivity after exposure to O_3 were unrelated to the presence of atopy.

König et al. (1980) exposed 14 healthy nonsmokers (13 men, 1 woman) for 2 hr to 0, 196, 627, and 1960 $\mu g/m^3$ (0.0, 0.10, 0.32, and 1.00 ppm) of O_3. Bronchial reactivity to ACh was determined after exposure. Significant increases in bronchial reactivity were observed with the ACh challenge following exposure to 627 $\mu g/m^3$ (0.32 ppm) and 1960 $\mu g/m^3$ (1.0 ppm) of O_3.

Bronchial reactivity of normal adult subjects was assessed by measuring the increase in SR_{aw} produced by inhalation of histamine aerosol (Dimeo et al., 1981). Seven subjects, intermittently exercising (15 min exercise, 15 min rest) at a load sufficient to double their resting $\dot{V}_E$, were exposed to 392 $\mu g/m^3$ (0.2 ppm) of O_3 over a 2-hr period. Two air exposures preceded the O_3 exposure, which was followed by another air exposure. Another group (five individuals) were only repeatedly tested pre- and post-air exposure for their response to histamine. In these two groups, the bronchial responsiveness to histamine was not different in the air exposures. The bronchomotor response to inhaled histamine aerosol was not altered following the 392-$\mu g/m^3$ (0.2-ppm) O_3 exposure. However, a third group (seven individuals) was also exposed to air for 2 days and to 784 $\mu g/m^3$ (0.4 ppm) of O_3 on the following day. The mean bronchial responsiveness to inhaled histamine was increased following exposure to 784 $\mu g/m^3$ (0.4 ppm) of O_3. Baseline SR_{aw} (i.e., before histamine) after the 0.4-ppm exposure remained unchanged.

As part of a study of repeated exposures to O_3 (discussed in detail in Section 10.3), Kulle et al. (1982b) exposed two separate groups of subjects (13 males, 11 females) for 3 hr to filtered air and then 1 week later to 784 $\mu g/m^3$ (0.4 ppm) of O_3. One hour before the end of exposure, 15 min of exercise at 100 W was performed approximating a $\dot{V}_E$ of four to five times resting values. Bronchial reactivity to methacholine was assessed after each exposure and was significantly enhanced ($P < 0.01$) in both subject groups following exposure to O_3 as compared to filtered-air exposure.

Two hypotheses have been proposed that are consistent with the observations of increased airway reactivity to histamine and methacholine following O_3 exposure (Holtzman et al., 1979). The first suggests that O_3 increases airway epithelial permeability, resulting in greater access of histamine and methacholine to bronchial smooth muscle and vagal sensory receptors. The second hypothesis suggests that O_3 or a byproduct of O_3 causes an increase in the number or the binding affinity of acetylcholine receptors on bronchial smooth muscle.

10.2.7 Mechanisms of Acute Pulmonary Effects

The primary acute respiratory responses to O_3 exposure are decrements in variables derived from measures of forced expiratory spirometry (volumes and flows) and respiratory symptoms (notably, cough and substernal pain upon deep inspiration). Altered ventilatory control during exercise (increased f_R and decreased V_T with $\dot{V}_E$ remaining unchanged) and small increases in airway resistance have also been observed.

Decrements in FVC observed at relatively high (1470-$\mu g/m^3$; 0.75-ppm) O_3 concentrations have been associated with increases in RV (Hazucha et al., 1973; Silverman et al., 1976). Since increased RV occurs only at higher O_3 concentrations, it has been postulated by Hazucha et al. (1973) that this increase results from gas trapping and premature airway closure caused by a direct effect of O_3 on small airway smooth muscle or by interstitial pulmonary edema.

At O_3 concentrations of 980 $\mu g/m^3$ (0.50 ppm) and less, decrements in FVC are related to decreases in TLC without changes in RV. Decreased TLC results from reductions in maximal expiratory position as indicated by the observation that inspiratory capacity also declines (Hackney et al., 1975c; Folinsbee et al., 1977b; Folinsbee et al., 1978). Moreover, a decrease in inspiratory effort, rather than a decrease in lung compliance, most likely causes the reduced inspiratory capacity resulting from O_3 exposure (Bates and Hazucha, 1973; Silverman et al., 1976; Folinsbee et al., 1978). Ozone is thought to "sensitize" or stimulate irritant (rapidly adapting) and possibly other airway receptors (Folinsbee et al., 1978; Golden et al., 1978; Holtzman et al., 1979; McDonnell et al., 1983). This results in vagally mediated inhibition of maximal inspiration, either involuntarily or due to discomfort (Bates et al., 1972; Silverman et al., 1976; Folinsbee et al., 1978; Adams et al., 1981). Stimulation of irritant receptors is also believed to be responsible for the occurrence of respiratory symptoms (Folinsbee et al., 1977b; McDonnell et al., 1983) and for alterations in ventilatory control (Folinsbee et al., 1975; Adams et al., 1981; McDonnell et al., 1983). These hypotheses remain to be proven.

Unless measured at absolute lung volumes, decrements in forced expiratory flows (e.g., $FEV_{1.0}$, $FEF_{25-75\%}$) are difficult to interpret. A small portion of the decrease in flow may be related to airway narrowing (Folinsbee et al., 1978; McDonnell et al., 1983). Airway narrowing, as indicated by increased airway resistance, probably results from either smooth-muscle contraction, mucosal edema, or secretion of mucus. These can be initiated by vagally mediated reflexes from irritant receptor stimulation, by the interaction of an endogenous or exogenous substance with the vagal efferent pathway, or by the direct action of O_3 (or an O_3-induced, locally released substance) on smooth muscle or mucosa (Folinsbee et al., 1978; Holtzman et al., 1979; McDonnell et al., 1983). Beckett et al. (1985) effectively blocked O_3-induced increases in airway resistance by having subjects breathe aerosols of atropine, a muscarinic cholinergic antagonist, prior to exposure. These findings support the conclusion that O_3-induced increases in airway resistance involve parasympathetic neural release of acetylcholine at the site of muscarinic receptors on the smooth muscle of large airways and suggest mediation of this response by vagal efferent reflex pathways.

It is probable that stimulation of airway receptors is an afferent mechanism common to changes in airway resistance as well as changes in volumes and flows. However, McDonnell et al. (1983) postulated the existence of more than one mechanism for the normal processing of this sensory input, implying that a different efferent mechanism is responsible for O_3-induced changes in lung volume. They based this postulation on their observed lack of correlation between individual changes in lung volumes and airway resistance and on differences in the concentration-response curves for these variables. Kulle et al. (1985) also observed a lack of correlation between individual changes in SG_{aw} and FVC ($r = 0.09$) and in SG_{aw} and FEV_1 ($r = 0.24$). Beckett et al. (1985) provide strong support for the involvement of more than one mechanism in O_3-induced pulmonary responses. While pretreatment with atropine blocked increased airway resistance in their O_3-exposed subjects, it had no effect on the O_3-induced decreases in lung volumes (FVC, TLC). Thus, while these findings indicate increased airway resistance is via a reflex stimulation of airway smooth muscle, the failure of atropine to block the decrease in lung volumes suggests a separate mechanism for this response which is not dependent on functioning muscarinic receptors.

10.2.8 Preexisting Disease

According to the National Health Interview Survey for 1979 (U.S. Department of Health and Human Services, 1981), there were an estimated 7,474,000 chronic bronchitics, 6,402,000 asthmatics, and 2,137,000 individuals with emphysema in the United States. Although there is some overlap of about 1,000,000 in these three categories, it can be reasonably estimated that over 15,000,000 individuals reported chronic respiratory conditions. In clinical studies that have been published, individuals with asthma or chronic obstructive lung disease (COLD) do not appear to be more responsive to the effects of O_3 exposure than are healthy subjects. Table 10-4 presents a summary of data from O_3 exposure in humans with pulmonary disease.

Linn et al. (1978) assessed pulmonary and biochemical responses of 22 asthmatics (minimal asthma to moderately severe chronic airway obstruction with limited disability) to 2-hr exposures to clean air, sham O_3, and 392 $\mu g/m^3$ (0.20 ppm) O_3 with secondary stressors of heat (31°C, 35 percent rh) and intermittent light exercise ($\dot{V}_E = 2 \times$ resting $\dot{V}_E$). Subjects continued the use of appropriate medication throughout the study. Evaluation of responses was not made in relation to the severity of the disorder present in these patients. After baseline (zero O_3) studies were completed, subjects were exposed to filtered air, a sham (i.e., some O_3 was initially present in the exposure chamber), and a 392- to 490-$\mu g/m^3$ (0.20- to 0.25-ppm) O_3 condition (a 3-day control study was conducted over 3 days [0 ppm O_3] on 14 of these individuals). During each 2-hr exposure condition, subjects exercised for the first 15 min

TABLE 10-4. OZONE EXPOSURE IN SUBJECTS WITH PULMONARY DISEASE

Ozone concentration μg/m³	Ozone concentration ppm	Measurement method[a,b]	Exposure duration and activity[c]	Observed effect(s)[d]	No. and description of subjects	Reference
196 627 1960	0.1 0.32 1.0	MAST, NBKI	2 hr R	No effect on SR$_{aw}$ and PaO_2; increased bronchial reactivity to ACh at 0.32 and 1.0 ppm in healthy subjects. SR$_{aw}$ increased following ACh challenge in 2/3 COLD subjects at 0.1 ppm.	3 COLD 1 asthma 14 healthy	König et al., 1980
235	0.12	UV, NBKI	1 hr IE (variable) @ 15-min intervals	No significant changes in forced expiratory performance or symptoms. Decreased SaO_2 during exercise was observed.	25 COLD	Linn et al., 1982a Hackney et al., 1983
235	0.12	UV	1 hr (mouthpiece) R	No significant changes in pulmonary function or symptoms.	10 asthma (adolescents)	Koenig et al., 1985
353 490	0.18 0.25	UV, NBKI	1 hr IE (variable) @ 15-min intervals	No significant changes in forced expiratory performance or symptoms. Group mean SaO_2 was not altered by O_3 exposure.	28 COLD	Linn et al., 1983
392	0.2	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	No significant changes in pulmonary function. Small changes in blood biochemistry. Increase in symptom frequency reported.	22 asthma	Linn et al., 1978
392 588	0.2 0.3	CHEM, NBKI	2 hr IE (28) for 7.5 min each half hour	No significant changes in pulmonary function or symptoms. SaO_2 decreased during exposure to 0.2 ppm.	13 COLD	Solic et al., 1982 Kehrl et al., 1983, 1985
392 588	0.2 0.3	UV, UV	40 min CE (40, graduated)	No significant changes in pulmonary function, exercise ventilation, cardiovascular response, or respiratory symptoms.	6 CHD	Superko et al., 1984
490	0.25	CHEM, NBKI	2 hr R	No significant effect on pulmonary function. $\dot{V}_{50}$ decreased in approximately 1/3 of the subjects demonstrating selective sensitivity to O_3.	17 asthma	Silverman, 1979
784	0.4	UV/CHEM, UV	3 hr/day 6 days IE(4-5xR) for 15 min	FVC and FEV_3 decreased on the first of five consecutive exposure days and with re-exposure.	20 smokers with chronic bronchitis	Kulle et al., 1984

[a] Measurement method: MAST = KI-Coulometric (Mast meter); CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry.

[b] Calibration method: NBKI = neutral buffered potassium iodide; UV = ultraviolet photometry.

[c] Activity level: R = rest; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min.

[d] See Glossary for the definition of symbols.

of each 30-min period. The exercise load was designed to double ventilatory volumes, but because of the relative physical condition of the subjects there was a wide variation in absolute $\dot{V}_E$ so that inhaled O_3 volume varied widely. Standard pulmonary function tests were performed pre- and post-exposure. No significant changes were noted except for a small change in TLC, which could have been explained by typical daily variations in this function. A slight increase in symptoms was also noted during O_3 exposures, but this increase was not statistically different from sham or control conditions. A spectrum of biochemical parameters was measured in blood obtained only post-exposure. The significant biochemical changes reported were small, and probably only represent the normally found individual and group variability seen in these parameters despite the investigators' suggestion that asthmatics may react biochemically at lower O_3 concentrations than nondiseased individuals.

Clinically documented asthmatics (16 years average duration of asthma) were exposed either to filtered air or 490 $\mu g/m^3$ (0.25 ppm) of O_3 for 2 hr while quietly resting (Silverman, 1979). Pulmonary functions were measured in these 17 asthmatics before and after exposure. Additional measurements of expiratory flow-volume and ventilation were made at half-hour intervals during the 2-hr exposures. The objective of the study was to study asthmatics irrespective of the severity of their disease under the best degree of control that could be achieved, i.e., in their normal conditions of life. Paired *t*-tests showed no significant changes in lung-function measures related to O_3. However, some individual asthmatics did respond to O_3 exposure with a decrease in lung function and an exacerbation of symptoms. One group of six subjects had demonstrable decreases in function, but information concerning the stage and/or development of their asthma was inadequately addressed. Such information would have been extremely valuable in providing opportunities to study this more susceptible portion of the asthmatic population further.

Koenig et al. (1985) exposed 10 adolescent asthmatics at rest to clean air and to 235 $\mu g/m^3$ (0.12 ppm) O_3. Exposure was via a rubber mouthpiece for 1 hr. The subjects, aged 11 to 18 years old, had a history of atopic (Type I, IgE mediated) extrinsic asthma, characterized by documented reversible airways obstruction, elevated serum IgE levels, positive reaction to inhaled dust, mites, mold and/or pollen antigens, and exercise-induced bronchospasm. Because of the relative severity of their asthma, subjects maintained their usual medication therapy during testing. A comparable group of 10 healthy, nonatopic adolescents, aged 13 to 18 years old, was also similarly exposed. No significant changes in pulmonary function or symptoms resulted from O_3 exposure as compared to exposure to clean air in either the healthy or asthmatic adolescent subjects.

Data from clinical studies have not indicated that asthmatics are more responsive to O_3 than are healthy subjects. However, the relative paucity of studies and some of the experimental design considerations (subject population, control of medication, exposure $\dot{V}_E$, appropriateness of pulmonary function measurements) in the three studies that have been published suggest that the responsiveness of asthmatics to O_3, relative to healthy subjects, may be an unresolved issue. (This issue is treated in more detail in Chapter 12).

Linn et al. (1982a) studied 25 individuals (46 to 70 years old) with COLD (emphysema and chronic bronchitis); 12 percent were nonsmokers and the remainder were moderate to heavy smokers, with 11 individuals not smoking at this time. All had chronic respiratory symptoms with subnormal forced expiratory flow rates; the mean FEV_1/FVC ratio was 50 percent. Each subject underwent a control filtered air and a 235-$\mu g/m^3$ (0.12-ppm) O_3 exposure (randomized) for 1 hr. These subjects first exercised for 15 min, then rested for 15 min, then exercised for 15 min, and finally rested for 15 min. Exercise loads were designed to elevate $\dot{V}_E$ to 20 L/min (the physiological cost of this exercise to each of the wide variety of subjects was not identified). Pre- and post-exposure measurements of various pulmonary functions as well as arterial oxygen saturation (SaO_2) (Hewlett-Packard ear oximeter) were made. No significant differences in forced expiratory performance or symptoms attributable to O_3 were found. From pre-exposure values at rest (normal saturations) to mid-exposure values during exercise, mean SaO_2 increased by 0.65 ± 2.28 percent with purified air, but decreased by 0.65 ± 2.86 percent with O_3. This difference was significant. However, this small decrement attributable to O_3 was near the limit of resolution of the oximeter and was detected by computer signal averaging; thus, its physiological and clinical significance is uncertain. Moreover, since many of the COLD subjects were smokers, interpreting changes in SaO_2 without knowing carboxyhemoglobin saturation (%COHb) is difficult. Preliminary reports of these same data have also been published (Hackney et al., 1983).

Solic et al. (1982) conducted a similar study of 13 COLD patients with the same age range (40 to 70 years) and with an approximately similar history as those used by Linn et al. (1982a). Their protocol consisted of two exposure days, one to filtered air (sham O_3) and one to 392 $\mu g/m^3$ (0.2 ppm) of O_3 in a randomized fashion. Subjects maintained their usual patterns of activity, drug use, etc., except for an imposition of no smoking for 1 hr prior to the baseline studies. During the 2-hr exposures, the subjects exercised for 7.5 min every half-hour at a load sufficient to increase $\dot{V}_E$ to 20 to 30 L/min and an oxygen uptake of ~1 L/min. SaO_2 was measured during the last exercise period. Pulmonary function measurements were made before and after exposure, with FVC maneuvers also obtained at 1 hr of exposure. There was no statistically significant difference between the effects of air exposure versus O_3 exposure in any of the spirometric measurement values or symptoms. The only significant alteration resulting from O_3 exposure was found in SaO_2, where decrements were reported in 11 of 13 subjects. Arterial saturation was 95.3 percent on filtered-air days and 94.8 percent on O_3 days. Again, knowledge of %COHb is necessary to interpret these small changes in SaO_2 correctly.

Kehrl et al. (1983) presented further information on individuals with COLD. They restudied eight subjects from the group that Solic et al. (1982) had exposed to 392 $\mu g/m^3$ (0.2 ppm) of O_3. In this experiment the subjects were exposed to 588 $\mu g/m^3$ (0.3 ppm) of O_3 with a protocol similar to that used by Solic et al. Data presented consisted of measurements made during the 392-$\mu g/m^3$ (0.2-ppm) exposure, as well as new data obtained during the 588-$\mu g/m^3$ (0.3-ppm) exposures. The second exposure occurred 6 to 9 months later. No statistically significant O_3-induced changes in respiratory mechanics or symptoms were found in the COLD patients at either O_3 concentration. Statistically significant changes in pulmonary function or symptoms were also not observed when the number of COLD patients exposed to 588 $\mu g/m^3$ (0.3 ppm) was increased to 13 (Kehrl et al., 1985). Arterial oxygen saturation (ear oximeter) measured in eight of these subjects during the last exercise interval was 0.95 percent less with O_3 exposure as opposed to clean air exposure; this difference nearly attained statistical significance ($P = 0.07$).

Linn et al. (1983) presented data on 28 COLD patients exposed for 1 hr to 0, 353, and 490 $\mu g/m^3$ (0.0, 0.18, and 0.25 ppm) of O_3. Subjects had chronic respiratory symptoms; their mean $FEV_{1.0}$/FVC was 58%, indicating a mild degree of obstruction for the group. Severity of COLD was classified as minimal for 12 subjects, moderate for 14 subjects, and severe for 2 subjects. Two subjects had never smoked, while eleven were ex-smokers and 15 were current smokers. Subjects continued use of chronic medication during the study but avoided inhaled bronchodilators on testing days. Subjects exercised for the first and third 15-min periods and rested in the second and fourth periods. The exercise performed varied in intensity as did the corresponding $\dot{V}_E$. Forced expiratory function and symptoms measured before and after exposure were not influenced by the exposures, confirming other reports that these individuals do not respond to O_3 exposures even at levels of O_3 exceeding first-stage alert levels. Arterial oxygen saturation (ear oximeter) was not changed during the second exercise period and post-exposure. Medication and severity of disease may explain the divergent results previously obtained. Differences may also be related to the level of exercise and the resulting ventilation. As a consequence, these patients may have inhaled comparatively small doses of O_3.

In all these studies on COLD patients, a wide diversity of symptoms and ventilatory deficits was present. The common findings by Linn and Solic as to small changes in SaO_2 may be of some significance, although they were not confirmed in subsequent studies at higher O_3 concentrations. The exercise performed in these studies was of very low intensity, and results from O_3 exposures where COLD patients exercised at higher intensities may be of interest.

König et al. (1980) performed studies on 18 individuals, three of whom suffered from COLD and one of whom had extrinsic allergic asthma (bronchial symptom free). The bronchial reactivity test used ACh as the test substance. Specific airway resistance was measured in the patients after a 2-hr exposure to 196 $\mu g/m^3$ (0.1 ppm) of O_3 as well as on a sham-exposure day. In two of the three patients with COLD, increases in SR_{aw} of 37 and 39 percent were recorded after the O_3 exposure. The asthmatic patient was not affected by exposure to this level of O_3. Whether the results presented represent the response to a bronchial reactivity test immediately post-exposure or to the O_3 exposure is unclear. In addition, the small number of COLD subjects studied makes an adequate evaluation difficult.

Kulle et al. (1984) exposed 20 chronic bronchitic smokers with some evidence of airway obstruction for 3 hr to filtered air and 804 $\mu g/m^3$ (0.41 ppm) of O_3. Fifteen minutes of bicycle exercise at 100 W was performed during the second hour of exposure. Forced vital capacity and FEV_3 decreased significantly with exposure to O_3 compared to clean-air exposure; the decreases were small in magnitude ($\leq$ 3 percent), and respiratory symptoms were mild.

One study (Superko et al., 1984) has attended the physiological responses of patients with ischemic coronary heart disease (n = 6) randomly exposed to 0, 392, and 588 μg/m^3 (0.0, 0.2, and 0.3 ppm) O_3. The diagnosis of coronary disease was made by documented previous myocardial infarction, angiography, or classic angina pectoris with reproducible ECG changes on graded exercise testing. Each patient had a well defined and reproducible symptomatic angina pectoris threshold. Three of the patients also exhibited evidence of obstructive pulmonary disease as indicated by $FEV_{1.0}$/FVC of less than 70 percent; smoking history of the subjects was not included. Each exposure was of 40 min duration and consisted of 10 to 15 min gradually incremented exercise warm-up followed by 25 to 30 min exercise at an intensity slightly below the subjects' symptom threshold (mean $\dot{V}_E$ = 42 L/min). Changes in pulmonary function (RV, FVC, $FEV_{1.0}$, FEF_{25-75}) following exposures were not different among the three conditions. Considering the magnitude of exercise $\dot{V}_E$ (42 L/min), changes in pulmonary function might have been expected. This lack of change may be related to the relatively short exposure duration, small number of subjects, or past smoking history of subjects. There were also no significant differences in cardiopulmonary responses ($\dot{V}_E$, f_R, $\dot{V}O_2$, HR, SBP) during exercise, time to onset of angina, or ischemic cardiovascular changes among the three conditions.

10.2.9 Other Factors Affecting Pulmonary Responses to Ozone

10.2.9.1 Cigarette Smoking. Smokers have been studied as a population group having potentially altered sensitivity to oxidant exposures. Hazucha et al. (1973) and Bates and Hazucha (1973) reported the responses of 12 subjects divided by smoking history (six smokers and six nonsmokers) who were exposed to 725 and 1470 μg/m^3 (0.37 and 0.75 ppm) O_3. These young (23.6 ± 0.7 years old) individuals alternated 15 min of exercise at twice resting ventilation and 15 min of rest during the 2 hr of the test. Pulmonary-function measurements were made after each exercise period. The characteristic odor of O_3 was initially detectable by all subjects, but they were unaware of it after one-half hour. Symptoms of typical oxidant exposures were reported by all subjects at the termination of exposure. Decrements in FVC and $FEF_{25-75\%}$ were greater for nonsmokers after either O_3 exposure, whereas smokers exhibited greater decrements in $FEV_{1.0}$ and 50% $\dot{V}_{max}$. Smokers exposed to 1470 μg/m^3 (0.75 ppm) of O_3 had a greater decrease in $FEF_{25-75\%}$ than did nonsmokers. The $FEF_{25-75\%}$ changes were much larger than the changes in $FEV_{1.0}$, regardless of O_3 concentration, exposure duration, and smoking habit. Smoking history (not given specifically) appeared to have different effects on the various pulmonary functions measured.

Kerr et al. (1975) exposed their subjects (10 smokers and 10 nonsmokers) to 980 μg/m^3 (0.5 ppm) of O_3 for 6 hr, during which time the subjects exercised twice for 15 min each ($\dot{V}_E$ = 44 L). For the remainder of the exposure time the subjects were resting. Follow-up measurements were made 2 and 24 hr later. A control day on which subjects breathed filtered air preceded the O_3-exposure day. The 24-hr post-exposure study was conducted in filtered air. Variance analyses were used to interpret the data. In nonsmokers, significant decrements in ventilatory function were observed following O_3 exposure, being most prominent for FVC and FEV_3. Similar significant decrements were observed for FEV_1 and maximum mid-expiratory flow. No decrements were observed in mean spirometry values in smokers as a group; in fact, all tests disclosed some degree of improvement, with significance at the 5 percent level for MEF. A significant reduction in SG_{aw} and increase in R_L were observed, for the most part in nonsmokers experiencing subjective symptoms. (All nonsmokers experienced one or more symptoms, while only 4 of 10 smokers had symptoms. These four smokers had been smoking for relatively short periods of time.)

Six subjects (three nonsmokers and three smokers of 20 cigarettes/day for 2 to 3 years) were studied by Kagawa and Tsuru (1979a). These subjects were exposed, no smoking on one day and smoking on another day, in either a filtered-air environment or one containing 588 μg/m^3 (0.3 ppm) of O_3. Two periods (10 min in duration) during the 2-hr exposure were devoted to smoking a cigarette. Smokers took one puff each minute (a total of 20 puffs) and nonsmokers took one puff every 2 min (a total of 10 puffs). Both groups reported a slight degree of dizziness and nausea after smoking. Measurements of SG_{aw} were obtained before and at the end of the first and second hours of exposure. Bronchial reactivity to an ACh challenge was determined pre- and post-exposure. The data presented in this report are minimal and sketchy, and statistical analyses are inadequate. One of the six subjects (a smoker) was a nonresponder to O_3. The remaining five responded in variable fashions, and direction of change could not be evaluated.

Kagawa (1983a) presented data on 5 smokers and 10 nonsmokers apparently exposed to 294 μg/m^3 (0.15 ppm) of O_3 for 2 hr to his standard intermittent rest-exercise regime. SG_{aw} was measured three times: at 1 and 2 hr during exposure and also at 1 hr post-exposure. Significant decreases were found during exposure, i.e., 4 percent at 1 hr and 10 percent at 2 hr in nonsmokers. No change from baseline occurred in the smokers. These data, which suggest significant differences in response between smokers and nonsmokers exposed to the low ambient level of 294 $\mu g/m^3$ (0.15 ppm) of O_3, were not presented in enough detail to permit in depth evaluation of the findings. Thus, the statistical significance, if any, of these findings is unclear.

DeLucia et al. (1983) reported that smokers (six men and six women) were relatively resistant to the oral inhalation of 588 $\mu g/m^3$ (0.3 ppm) of O_3. Few smokers detected the presence of O_3, whereas the majority of nonsmokers (six men and six women) experienced significant discomfort. Pulmonary function tests (FVC, FEV, and $FEV_{25-75\%}$) were made pre- and post-exposure (within 15 min). Overall, the decrements in pulmonary functions were significant and the authors attributed them to O_3. The relative insensitivity of smokers based on these three measurements was indicated by the decrements of 5.9 to 12.9 percent in nonsmokers, whereas smokers had 1.2 to 9.0 percent diminutions in these functions. Additional analyses of their pulmonary function data suggested that women nonsmokers were more sensitive to 588 $\mu g/m^3$ (0.3 ppm) of O_3 than women smokers. No apparent differences were noted for the men.

Thirty-two moderate or heavy smoking subjects (26 men and 6 women) were divided into four groups and exposed randomly to air alone, air plus smoking (2 cigarettes/hr), O_3 alone, and O_3 plus smoking (Shephard et al., 1983). Four O_3-exposure protocols were employed: 725 $\mu g/m^3$ (0.37 ppm) and 1470 $\mu g/m^3$ (0.75 ppm) in subjects at rest; and 980 $\mu g/m^3$ (0.50 ppm) and 1470 $\mu g/m^3$ (0.75 ppm) with the subjects exercising during the last 15 min of each half hour (the first 15 min of each period were at rest) for the 2-hr exposure. Carboxyhemoglobin was determined indirectly with the initial value being 1.61 percent. In nonsmoking days, COHb decreased, while on smoking days COHb increased by as much as 1.14 percent above the initial value. The increase in COHb was significantly lower on those days when smoking was conducted in an O_3 environment. Ozone exposure alone (no smoking during exposure) resulted in the typical and anticipated decreases in pulmonary functions (FVC, $FEV_{1.0}$, 25% $\dot{V}_{max}$, and 50% $\dot{V}_{max}$) as reported by others. However, the onset of these pulmonary changes was slower and the response less dramatic compared to data obtained on nonsmokers. The authors offered two explanations to account for the diminished response: (a) the presence of increased mucus secretion by these chronic smokers may have offered transient protection against O_3's irritant effect or

(b) the sensitivity of the airway receptors may have been reduced by chronic smoking. The chronic effect of smoking induced a delay in the bronchial irritation response to O_3 exposure. There was no significant interaction between cigarette smoking and responses to O_3.

10.2.9.2 Age and Sex Differences. Although a number of controlled human exposures to O_3 have used both male and female subjects of varying ages, in most cases the studies have not been designed to determine age or sex differences. In fact, normal young males usually provide the subject population, and where subjects of differing age and sex are combined, the groups studied are often too small in number to test for potential differences reliably.

Adams et al. (1981) attempted to examine the effects of age on response to O_3 in a small number (n=8) of nonsmoking males varying in age from 22 to 46 years. Comparison of the mean change in pulmonary function between the three oldest subjects (33 to 46 years old) and the five youngest subjects (22 to 27 years old) revealed only small, inconsistent differences.

McDonnell et al. (1985b) exposed boys (n = 23), aged 8 to 11 yr, once to 0.0 and once to 235 $\mu g/m^3$ (0.12 ppm) O_3 in random order. The exposure protocol was identical to that previously employed in their study of adult males (McDonnell et al., 1983). Exposure duration was 150 min, and the subjects alternated 15-min periods of rest and heavy exercise ($\dot{V}_E$ = 35 L/min/m^2 BSA) during the first 120 min of exposure. Forced expiratory spirometry and respiratory symptoms were measured before and at 125 min of exposure; airway resistance was measured before and at 145 min of exposure. Definitive statistical analyses (paired t-tests) were restricted to testing changes in $FEV_{1.0}$ and cough since these variables demonstrated the most statistically significant changes in their previous study of adults. Exploratory statistical analyses were performed for changes in the other measured variables; however, these analyses cannot be interpreted as tests of hypotheses. When compared with air exposure, a small (3.4 percent) but significant decrement in $FEV_{1.0}$ was observed, and exploratory analyses suggest that decrements in FVC and forced expiratory flow rates may also have occurred. No significant increase in cough was found due to O_3 exposure, and the other exploratory functions and symptoms did not change. Results from this study of boys were compared to those of adult males exposed under identical conditions (McDonnell, 1985c). Actually, exercise $\dot{V}_E$ was less in the children (39 L/min) than in the adults (65 L/min), however, when normalized for BSA, both children and adults were exercising at similar ventilation rates ($\dot{V}_E$/BSA of ≅ 35 L/min/m^2). Statistical comparisons of the O_3 effects between children and adults were not performed due to the repeated measures design in the children's study and the use of independent samples in the adult study. With exposure to 235 μg/m^3 (0.12 ppm) O_3, $FEV_{1.0}$ decreased 3.4 percent for the children as compared to a 4.3 percent decrease for the adults. Exposure to O_3 caused an increase in cough reported by adults while children experienced little or no increase in cough after O_3 exposure. These results indicate that the effects of O_3 exposure on lung spirometry were very similar for both adults and children. However, adults had an increase in cough as a result of exposure, while children reported no symptoms. The reason for this difference is not known and needs further study.

Folinsbee et al. (1975), noting the lack of enough subjects for adequate subdivision, attempted to make sex comparisons in a group of 20 male and 8 female subjects exposed to O_3. No significant differences could be shown in either symptomology or physiological measurements between male and female subjects.

Horvath et al. (1979) studied eight male and seven female subjects exposed for 2 hr to 0, 490, 980, and 1470 μg/m^3 (0, 0.25, 0.50, and 0.75 ppm) of O_3. Forced expiratory function decreased immediately following exposure to 980 and 1470 μg/m^3 (0.50 and 0.75 ppm), with greater changes occurring at the highest O_3 concentration. The average decrements in $FEV_{1.0}$ were 3.1 and 10.8 percent, respectively, for men, compared to 8.6 and 19.0 percent for women. Although the data suggested that there may be potential sex differences in the extent of changes in lung function due to O_3 exposure, the results of an analysis of variance for sex differences were not presented.

Gliner et al. (1983) presented data on 8 male and 13 female subjects exposed for 2 hr on five consecutive days to 0, 392, 392, 392, and 823 or 980 μg/m^3 (0, 0.20, 0.20, 0.20, and 0.42 or 0.50 ppm) of O_3, respectively. During exposure the subjects alternated 15 min of rest with 15 min of exercise on a bicycle ergometer at loads sufficient to produce expired ventilations of approximately 30 L/min for men and 18 L/min for women. Forced expiratory measurements of FVC, $FEV_{1.0}$, and $FEF_{25-75\%}$ indicated that prior exposure to 392 μg/m^3 (0.20 ppm) of O_3 had no effect on functional decrements occurring after subsequent exposure to either 823 or 980 μg/m^3 (0.42 or 0.50 ppm) of O_3 on the fourth day (see Section 10.3). Although differences between men and women were reported for all three measurements, with men having expected larger expired volumes and flows, there were no gender by pollutant interactions, indicating that male and female subjects responded to O_3 in a similar fashion.

DeLucia et al. (1983) reported on 12 men and 12 women (equally divided by smoking history) exercising for 1 hr at 50 percent of their max $\dot{V}O_2$ while breathing 588 $\mu g/m^2$ (0.3 ppm) of O_3 through a mouthpiece. Minute ventilation for the men averaged 51 L/min and for the women 34.7 L/min. Women nonsmokers who did not inhale as much O_3 as nonsmoking men reported approximately a fourfold increase in symptoms, while smoking women had less severe symptomatic responses than smoking men. Although significant decrements in pulmonary function were found for FVC (6.9 percent), $FEV_{1.0}$ (7.9 percent), and $FEF_{25-75\%}$ (12.9 percent), there were no significant differences between the sexes. These investigators also found increases in f_B and decreases in V_T during exercise. These effects are similar to those reported by other investigators.

Gibbons and Adams (1984) reported the effects of exercising 10 young women for 1 hr at 66 percent of max $\dot{V}O_2$ while the women breathed 0, 297, or 594 $\mu g/m^3$ (0, 0.15, or 0.30 ppm) of O_3. Significant decrements in forced expiratory function were reported at 594 $\mu g/m^3$ (0.30 ppm) of O_3. Comparison of these effects with the results from male subjects previously studied by the authors (Adams et al., 1981) indicated that the women appeared to be more responsive to O_3 even though the men received a greater effective dose than the women. However, large individual variations in responsiveness were present in all groups.

The possible enhancement of responses to O_3 inhalation in female subjects was investigated in the same laboratory (Lauritzen and Adams, 1985). Comparisons between the sexes were made on a equivalent effective dose basis (O_3 concentrations x $\dot{V}_E$ x exposure duration). Six young women exercised continuously for 1 hr at three exercise levels (23, 35, and 46 L/min) while being exposed to 0, 392, 588, and 784 $\mu g/m^3$ (0.0, 0.2, 0.3, and 0.4 ppm) O_3. Significant, O_3-dependent decrements were observed for FVC, FEV_1, and FEF_{25-75} along with changes in the exercise ventilatory pattern (i.e., increased f_R and decreased V_T). A comparison of these effects with the responses reported in an equal number of young adult males previously studied by the authors (Adams et al., 1981) at the same total O_3 effective doses revealed significantly greater effects on FVC, FEV_1, and f_R for the females. Many, but not all, of the gender differences were lost when responses were normalized for "relative effective dose." The ratio of $\dot{V}O_2$ max or TLC in males compared to females was 0.68 and 0.69, respectively. Thus, when responses were expressed at the same relative exercise intensity or as dose per unit TLC, the gender differences were diminished. Sample sizes were too small (n=6), however, to quantitatively identify other specific factors that could account for the apparent differences between male and female subjects exposed to O_3.

10.2.9.3 Environmental Conditions. Very few controlled human studies have addressed the potential influence environmental conditions such as heat or relative humidity (rh) may have on responses to O_3. In fact, most exposures have been performed under standard room temperature and humidity conditions (20-25°C, 45-50 percent rh). A series of studies by Hackney et al. (1975a,b,c; 1977a) and Linn et al. (1978) were conducted at a higher temperature and lower humidity (31°C, 35 percent rh) to simulate ambient environmental conditions during smog episodes in Los Angeles. No comparisons were made to the effects from O_3 exposure at standard environmental conditions in other controlled studies.

Folinsbee et al. (1977b) studied the effects of a 2-hr exposure to 980 $\mu g/m^3$ (0.5 ppm) of O_3 on 14 male subjects under four separate environmental conditions: (1) 25°C, 45 percent rh; (2) 31°C, 85 percent rh; (3) 35°C, 40 percent rh; and (4) 40°C, 50 percent rh. Wet bulb globe temperature (WBGT) equivalents were 64.4, 85.2, 80.0, and 92.0°F, respectively. The subjects exercised for 30 min at 40 percent of their max $\dot{V}O_2$ (Section 10.2.2 and Figure 10-1). Decreases in vital capacity and maximum expiratory flow during O_3 exposure were most severe immediately after exercise. There was a trend for a greater reduction when heat stress and O_3 exposure were combined (WBGT=92.0°F), but this effect was only significant for FVC. In a similar study with eight subjects exposed to 980 $\mu g/m^3$ (0.5 ppm) of O_3 plus 940 $\mu g/m^3$ (0.5 ppm) of nitrogen dioxide (NO_2) (Folinsbee et al., 1981) (Section 10.6.3), the effects of heat and pollutant exposure on FVC were found to be no greater than additive. Part of the modification of O_3 effects by heat stress was attributed to increased ventilation since ventilatory volume and tidal volume increased significantly at the highest thermal condition studied (40°C, 50 percent rh).

More recently, Gibbons and Adams (1984) had 10 trained and heat-acclimated young women exercise for 1 hr at 66 percent of their maximum oxygen uptake while breathing either 0.0 $\mu g/m^3$ (0.0 ppm), 297 $\mu g/m^3$ (0.15 ppm), or 594 $\mu g/m^3$ (0.30 ppm) of O_3. These studies were conducted at two ambient conditions, i.e. 24° or 35°C. (Whether these are only dry bulb (db) temperatures or represent WBGT values is unclear, since humidity was not reported). No significant changes in any measured function were observed at 0 $\mu g/m^3$ (0.00 ppm) or

297 μg/m^3 (0.15 ppm) of O_3. Significant reductions in FVC, $FEV_{1.0}$, TLC, and $FEF_{25-75\%}$ ($P < 0.004$) were reported as a consequence of exercising at 594 μg/m^3 (0.30 ppm). Pre-post decrements in FVC, $FEV_{1.0}$, and $FEF_{25-75\%}$ in the 0.30 ppm, 24°C environment were 13.7, 16.5, and 19.4 percent respectively, compared to observed decrements of 19.9, 20.8, and 20.8 percent, respectively, in the 0.30-ppm O_3 and 35°C condition. Only FVC differed significantly between the two temperature conditions. Some subjects failed to complete the exercise period in 35°C and 0.30 ppm O_3, and one subject could not finish the exercise in 24°C and 0.30 ppm O_3. Subjects reported more subjective discomfort, (cough, pain on inspiration, throat tickle, dizziness, and nausea) as O_3 concentrations increased. No other effects were reported, although it was observed that O_3 (0.30 ppm) exposure and ambient high temperature induced an interactive effect on $\dot{V}_A$ and f_R.

10.2.9.4 Vitamin E Supplementation. The possible protective effects of vitamin E against short-term responses to O_3 exposure have not been as extensively investigated in humans as they have in animals (see Chapter 10). Only two studies have been published on the pulmonary effects of vitamin E supplementation in healthy subjects exposed to O_3. Both of these have failed to show any protective effect against O_3-induced changes in respiratory symptoms and lung function (Hackney et al., 1981) or against *in vivo* lipid peroxidation of the lung, as measured by decreased pentane production (Dillard et al., 1978). Additional studies demonstrating the lack of significant differences between the extrapulmonary responses of vitamin-E supplemented and placebo groups exposed to O_3 are discussed in Section 10.6.

Dillard et al. (1978) studied ten vitamin E-sufficient adults breathing filtered air or 588 μg/m^3 (0.3 ppm) O_3 on a mouthpiece while continuously exercising for 1 hr at 50 percent $\dot{V}O_{2max}$. Pulmonary function was measured before and after each exercise period. Expired air samples were collected from five subjects at rest, after 5 min of exercise while breathing air, and after 5, 15, 30, 45, and 60 min of exercise while breathing O_3. Expired pentane, an index of lipid peroxidation, was measured during the pre- and postexercise resting periods by gas chromatography. Exposure to O_3 caused a significant increase in RV and significant decreases in VC and $FEV_{1.0}$. All subjects reported throat tickle associated with O_3 while some subjects experienced symptoms such as chest tightness, cough, pain on deep inspiration, congestion, wheezing, or headache. Exercise alone resulted in an increased production of pentane. However, there was no change in pentane production as a result of exposure to 0_3 above that caused by the stress of exercise.

In a separate experiment, Dillard et al. (1978) tested six subjects exposed to hydrocarbon-scrubbed air during an initial 5-min rest, during graded exercise (25, 50, and 75 percent $\dot{V}0_{2max}$) for 20, 40, and 60 min, and during a 20-min postexposure rest period. The same exercise protocol was repeated after supplementation of the subjects with 400 IU dl-α-tocopherol three times a day for 2 weeks, which increased plasma tocopheral levels 240 percent. This treatment significantly reduced expired pentane levels at rest and during exercise. No significant differences in pulmonary function were obtained in response to 1 hr of exercise before and after vitamin E supplementation.

Hackney et al. (1981) studied the effects of a 2-hr exposure to filtered air or 980 $\mu g/m^3$ (0.5 ppm) 0_3 in healthy subjects (9 males and 25 females) receiving either 800 IU dl-α-tocopherol (n = 16) or a similar appearing placebo (n = 18) daily for 9 or 10 weeks. Mean serum vitamin E concentration increased by 70 percent over this period in the supplemented group while the mean concentration in the placebo group did not change significantly. During exposure, the subjects alternated 15-min periods of rest and exercise at two times resting ventilation. Pulmonary function and respiratory symptoms were evaluated at the end of each exposure. No significant effects of vitamin E supplementation were found; however, a few of the supplemented male subjects showed a possible beneficial effect. Since the sample size of male subjects was small (n = 9), a follow-up study was performed. Subjects received either 1600 IU of dl-α-tocopherol (n = 11) or placebo (n = 11) daily for 11 or 12 weeks. The mean serum vitamin E concentration increased by 140 percent in the supplemented group and 30 percent in the placebo group. Exposures took place on three successive days during the last week of supplementation. The subjects were exposed to filtered air for 2 hr on the first day, followed by 2-hr exposures to 980 $\mu g/m^3$ (0.5 ppm) 0_3 on the second and third days. The exercise protocol during exposure was similar to that described above. Pulmonary function and respiratory symptoms were evaluated at the end of each exposure. Ozone caused significant decreases in FVC, $FEV_{1.0}$, $FEV_{25\%}$, $FEF_{50\%}$, ΔN_2, and TLC in both the vitamin E-supplemented and placebo groups. The mean changes were not significantly different between groups. Although symptoms did not significantly increase with 0_3 exposure, there were no differences between the vitamin E and placebo groups. Results from these studies do not support a protective effect of vitamin E supplementation against short-term pulmonary responses in human subjects exposed to O_3.

10.3 PULMONARY EFFECTS FOLLOWING REPEATED EXPOSURE TO OZONE

Just as pulmonary function decrements following a single exposure to O_3 are well documented, several studies of the effects of repeated daily exposures to O_3 have also been completed (Table 10-5). In general, results from these studies indicate that with repeated daily exposures to O_3, decrements in pulmonary function are greatest on the second exposure day. Thereafter, on each succeeding day decrements are less than the day before, and on about the fifth exposure day small decrements or no changes are observed. Following a sequence of repeated daily exposures, there is a gradual time-related return of the susceptibility of pulmonary function to O_3 exposure similar to that observed prior to repeated exposures. Repeated daily exposure to a given low concentration of O_3 does not affect the magnitude of decrement in pulmonary function resulting from exposure at higher O_3 concentration.

All the reported studies of repeated responses to O_3 have used the term "adaptation" to describe the attenuation of decrements in pulmonary function that occurs. Unfortunately, since the initial report of such attenuation used adaptation, each succeeding author chose not to alter the continued use of this selected term. In the strict sense, adaptation implies that changes of a genetic nature have occurred as a result of natural selection processes, and as such, use of adaptation in the prior context is a misnomer.

Other terms (acclimation, acclimatization, desensitization, tolerance) have been recommended to replace adaptation and perhaps are more suitable. However, the correct use of any of these terms requires knowledge of (1) the physiological mechanisms involved in the original response, (2) which mechanisms are affected and how they are affected to alter the original response, and/or (3) whether the alteration of response is beneficial or detrimental to the organism. The present state of knowledge is such that we do not fully understand the physiological pathway(s) whereby decrements in pulmonary function are induced by O_3 exposure, and of course, the pathways involved in attenuating these decrements and how they are affected with repeated O_3 exposure are even less understood. Moreover, while attenuation of O_3-induced pulmonary

TABLE 10-5. CHANGES IN LUNG FUNCTION AFTER REPEATED DAILY EXPOSURE TO AMBIENT OZONE

Ozone Concentration		Measurement[a,b] method	Exposure duration and activity[c]	No. of subjects	Percent change in $FEV_{1.0}$ on consecutive exposure days					References
µg/m³	ppm				First	Second	Third	Fourth	Fifth	
392	0.2	CHEM, NBKI	2 hr, IE(30)	10	+1.4	+2.7	-1.6	---	---	Folinsbee et al., 1980
392	0.2	UV, UV	2 hr, IE(18 & 30)	21	-3.0	-4.5	-1.1	---	---	Gliner et al., 1983
392	0.2	UV, UV	2 hr, IE(18 & 30)	9[d]	-8.7	-10.1	-3.2	---	---	Gliner et al., 1983
686	0.35	CHEM, NBKI	2 hr, IE(30)	10	-5.3	-5.0	-2.2	---	---	Folinsbee et al., 1980
784	0.4	CHEM, NBKI & MAST, NBKI	3 hr, IE(4-5 x R)	14	-10.2	-14.0	-4.7	-3.2	-2.0	Farrell et al., 1979
784	0.4	CHEM, NBKI & MAST, NBKI	3 hr, IE(4-5 x R)	13[e]	-9.2	-10.8	-5.3	-0.7	-1.0	Kulle et al., 1982b
784	0.4	CHEM, NBKI & MAST, NBKI	3 hr, IE(4-5 x R)	11[e]	-8.8	-12.9	-4.1	-3.0	-1.6	Kulle et al., 1982b
784	0.4	UV, NBKI	2 hr, IE(2 x R)	7[f]	↑↑↑	↑	0			Dimeo et al., 1981
804	0.41	CHEM, NBKI & UV, UV	3 hr, IE(4-5 x R)	20[g]	-2.8	-0.9	0	-0.6	-1.1	Kulle et al., 1984
823	0.42	UV, UV	2 hr, IE(30)	24	-21.1	-26.4	-18.0	-6.3	-2.3	Horvath et al., 1981
921	0.47	UV, UV	2 hr, IE(3 x R)	11(7)[h]	-11.4	-22.9	-11.9	-4.3	---	Linn et al., 1982b
980	0.5	CHEM, NBKI	2 hr, IE(30)	8	-8.7	-16.5	-3.5	---	---	Folinsbee et al., 1980
980	0.5	CHEM, NBKI	2.5 hr, IE(2 x R)	6	-2.7	-4.9	-2.4	-0.7	---	Hackney et al., 1977a

[a] Measurement methods: MAST = KI-coulometric (Mast meter); CHEM = gas-phase chemiluminescence, UV = ultraviolet photometry.

[b] Calibration methods: NBKI = neutral buffered potassium iodide; UV = UV photometry.

[c] Exposure duration and intermittent exercise (IE) intensity were variable; minute ventilation ($\dot{V}_E$) given in L/min or as a multiple of resting ventilation.

[d] Subjects especially sensitive on prior exposure to 0.42 ppm O_3 as evidenced by a decrease in $FEV_{1.0}$ of more than 20%. These nine subjects are a subset of the total group of 21 individuals used in this study.

[e] Bronchial reactivity to a methacholine challenge was also studied.

[f] Bronchial reactivity to a histamine challenge (no data on $FEV_{1.0}$). SR_{aw} measured (↑). Note that on third day histamine response was equivalent to that observed in filtered air (see text).

[g] Subjects were smokers with chronic bronchitis.

[h] Seven subjects completed entire experiment.

function decrements appears to reflect protective mechanisms primarily directed against the acute and subchronic effects of the irritant, Bromberg and Hazucha (1982) have also speculated that this attenuation may reflect more severe effects of O_3 exposure, such as cell injury. Therefore, in the following discussion of specific studies, results will be presented without use of a specific term to describe observed phenomena generally. The use of response to imply pulmonary decrements resulting from O_3 exposure and changes in response or responsiveness of the subject to imply alterations in the magnitude of these decrements will be retained.

Hackney et al. (1977a) performed the initial experiments that demonstrated that repeated daily exposures to O_3 resulted in augmented pulmonary function responses on the second exposure day and diminution of responses after several additional daily exposures. Six subjects who in prior studies had demonstrated responsiveness to O_3 were studied during a season of low smog to minimize potential effects from prior O_3 exposure. All but one subject had a history of allergies. They were exposed for approximately 2.5 hr to 980 $\mu g/m^3$ (0.5 ppm) of O_3 for four consecutive days after one sham exposure. Ambient conditions in the chamber were 31°C db and 35 percent rh. During the first 2 hr, light exercise (of unknown level) was performed for 15 min every 30 min. The last half hour was used for pulmonary testing. Small decrements occurred in FVC and FEF_{75} and differed among the five test days. Additional statistical evaluation showed that these differences were related to the larger decrements in function observed on the second O_3 exposure day. Other pulmonary functions, i.e., total airway resistances (R_t) and nitrogen washout (ΔN_2), also improved on latter exposure days, but the differences were not statistically significant. The pattern of change clearly indicated that subjects had lesser degrees of pulmonary dysfunction by the third day of exposure, and these functions were nearly similar on day 4 to values found on the pre-exposure day to filtered air. In this small subject population, considerable variability in responses was noted (one subject with no history of allergies showed no pulmonary decrements, while another subject had a large reduction in FVC and FEV_1 and an increase in ΔN_2 on day 2 with a return of responses to near control levels on day 4).

Farrell et al. (1979) investigated the pulmonary responses of 14 healthy nonsmoking (10 men and 4 women) subjects to five consecutive, daily 3-hr exposures to filtered air or O_3. In the first week, subjects were studied in a filtered-air environment, followed in a second week with exposures to 784 μg/m^3 (0.4 ppm) of O_3. Pulmonary function (FVC, FEV_1, FEV_3, SG_{aw}, and FRC) was determined at the end of the 3-hr exposures. One bout of exercise ($\dot{V}_E$ measured on one subject = 44 L/min) was performed after 1.5 hr of exposure. Statistical evaluations used a repeated measures analysis of variance for significant differences between the control and O_3 exposure weeks, using each day of each exposure to make the comparisons. The analysis of variance showed that FVC, FEV_1, FEV_3, and SG_{aw} differed significantly between control and O_3 exposure weeks. No changes in FRC were found. In the O_3 exposure, SG_{aw} decreased significantly only on the first 2 days; this response was similar to air exposure day values on the last 3 days. Significant decreases in FVC occurred on the first three days only; however, the decrements were significantly greater on the second day than on the first. Decrements in $FEV_{1.0}$ and $FEV_{3.0}$ were substantial on the first day and increased on the second day of exposure. These decrements diminished to air exposure levels by the third day ($FEV_{3.0}$) and fourth day ($FEV_{1.0}$) of O_3 exposures. The severity of symptoms generally corresponded to the magnitude of pulmonary function changes. Symptoms were maximal on the first 2 days, decreasing thereafter with only one subject being symptomatic on the final day of exposure to O_3. Reporting of symptoms was maximal on the second O_3 day. These investigators noted that five consecutive days of exposure (10 subjects) to 588 μg/m^3 (0.3 ppm) of O_3 failed to induce significant changes in FVC or SG_{aw}, implying that measurable changes are likely to occur in pulmonary function at O_3 concentrations between 588 and 784 μg/m^3 (0.30 and 0.4 ppm) with 2 hr of exposure at these exercise levels.

Folinsbee et al. (1980) exposed healthy adult males for 2 hr in an environmental chamber at 35°C and 45 percent rh to filtered air on day 1, to O_3 on days 2 through 4, and to filtered air on day 5. Three groups of subjects were used, each exposed to a different concentration of O_3: group 1 (n=10), 392 μg/m^3 (0.20 ppm) of O_3; group 2 (n=10), 686 μg/m^3 (0.35 ppm) of O_3; group 3 (n=8), 980 μg/m^3 (0.50 ppm) of O_3. Subjects alternately rested and exercised at a $\dot{V}_E$ of 30 L/min for 15-min periods. There were no significant acute or cumulative effects of repeated exposure to 392 μg/m^3 (0.20 ppm) of O_3. With exposure to 686 μg/m^3 (0.35 ppm) of O_3, decrements in forced expiratory variables appeared on the first O_3 exposure day. Similar decrements occurred on the second O_3 exposure day, although there was no significant difference in responses observed on the first two exposure days. On the third day of exposure the pulmonary function changes were of lesser magnitude than on the first

2 days. In group 3, marked decrements in pulmonary function occurred ($FEV_{1.0}$ decreased 8.7 percent) after the first exposure to 980 μg/m^3 (0.50 ppm) of O_3; these decrements were even greater ($FEV_{1.0}$ decreased 16.5 percent) after the second O_3 exposure (Figure 10-3). While not totally abolished, an attenuation of these decrements ($FEV_{1.0}$ decreased 3.6 percent) was observed following the third O_3 exposure. The subjects claimed the most discomfort for the second O_3 exposure. Many noted marked reductions in symptoms on the third consecutive day of exposure to O_3. Two additional subjects were exposed to 980 μg/m^3 (0.50 ppm) of O_3 for four consecutive days. Although effects of O_3 on pulmonary function were observed on the first two days of exposure, few effects were seen on the third day, and no effect was observed on the fourth day. The authors concluded that there were some short-term (2-day) cumulative effects of exposure to concentrations of O_3 that produced acute functional effects. This response period was followed by a period in which there was a marked lessening of the effect of O_3 on pulmonary function and on the subjective feelings of discomfort associated with exposure to O_3. The subjects for these studies represented a broad population mix in that some subjects had a prior history of respiratory difficulties, some essentially had no past respiratory history, and approximately two-thirds had prior experience with pollutant exposure.

Horvath et al. (1981) performed studies designed not only to determine further the influence of five consecutive days of exposure to 823 μg/m^3 (0.42 ppm), but to estimate the persistence of the attenuation of pulmonary responses. During the 125 min of exposure, 24 male subjects alternately rested and exercised ($\dot{V}_E$ = 30 L/min) for 15-min periods. Measurements of pulmonary functions were made daily pre- and post-exposure. A filtered-air exposure was conducted during the week prior to the O_3 exposures. Selected subjects were then randomly assigned to return after 6 to 7, 10 to 14, and 17 to 21 days for a single exposure to O_3. Ambient O_3 levels in the locations where the subjects lived seldom exceeded 235 μg/m^3 (0.12 ppm). The major pulmonary function measurements made and subjected to statistical analysis on these subjects were FVC, FEV_1, and $FEF_{25-75\%}$. Changes with time in all three measurements were similar and major emphasis was directed toward FEV_1 changes. Significant interaction effects occurred between the two within-subject factors (day of exposure and pre- and post-exposure change in FEV_1). The interaction resulted primarily from the post-exposure FEV_1 data, which revealed a "U"-shaped pattern across

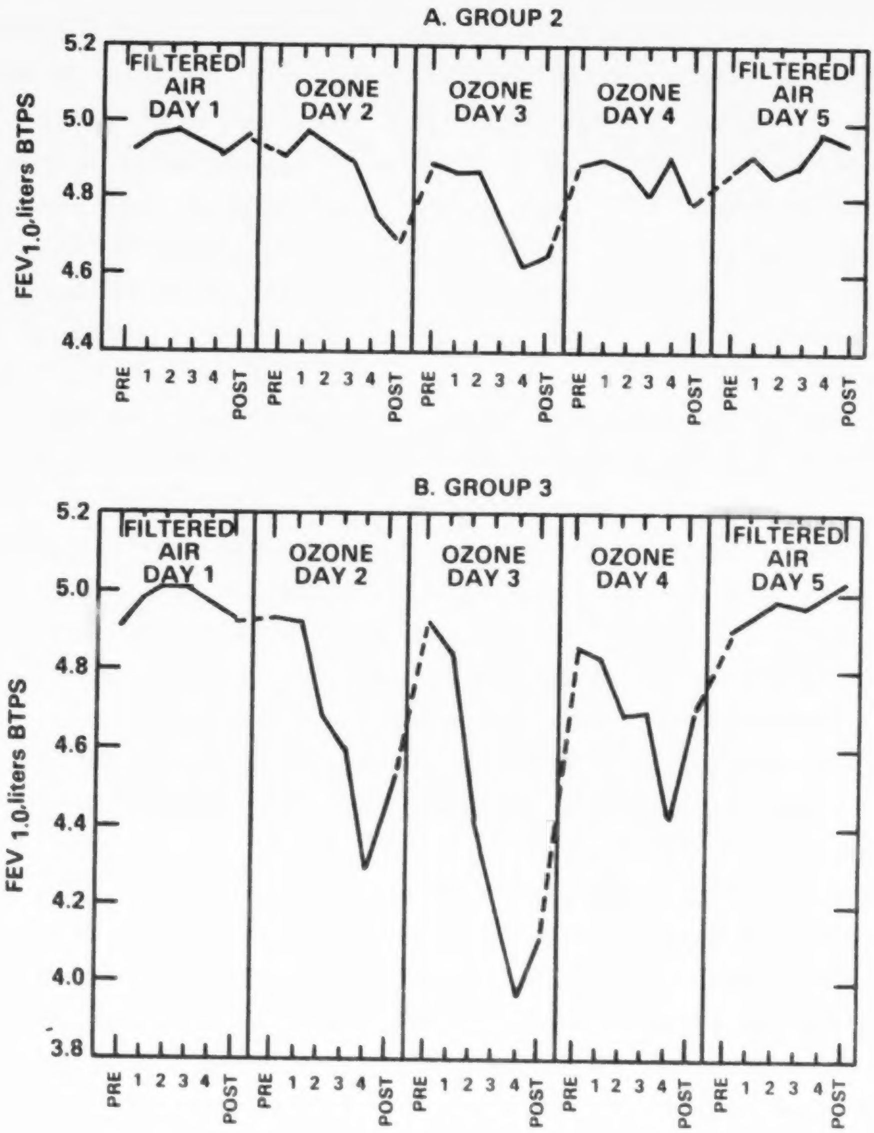

Figure 10-3. Forced expiratory volume in 1-sec ($FEV_{1.0}$) in two groups of subjects exposed to (A) 0.35 ppm ozone, and (B) 0.50 ppm ozone, for 3 successive days. Numbers on the abscissa represent successive half-hour periods of exposure.

Source: Folinsbee et al. (1980).

days during O_3 exposure. A significant decline appeared on day 1 (+1.7 to -63 percent, mean = -21 percent), and a greater significant decline appeared on day 2 (-26.4 percent). On day 3 the decrement in FEV_1 had returned to that observed on day 1, but it was still significantly greater than during room air exposure. The decrements in FEV_1 from preexposure to postexposure on days 4 and 5 were no longer significant although the absolute value of postexposure FEV_1 continued to be significantly less than the initial filtered air exposure. Subjective symptoms followed a similar pattern, with subjects on the fifth day indicating that they had not perceived any O_3. Two subjects showed little attenuation of response to O_3, and one subject was not affected by the O_3 exposures. Subjects who were more responsive on the first day of exposure required more consecutive days of daily exposure to attenuate response to O_3. All 24 subjects returned for an additional exposure to O_3 from 6 to 21 days later; of these, only 16 were considered to be sensitive to O_3, and their data are shown in Figure 10-4. Although the number of subjects in each repeat exposure was small, it was apparent that attenuation of response did not persist longer than 11 to 14 days, with some loss occurring within 6 to 7 days. In general, these authors made some interesting observations: (1) the time required to abolish pulmonary response to O_3 was directly related to the magnitude of the initial response; (2) the time required for attenuation of pulmonary responses to occur was apparently inversely related to the duration of attenuation and (3) in one individual, attenuation of pulmonary response to O_3 persisted up to 3 weeks. The mechanism responsible for attenuation of response was not elucidated, although two mechanisms were postulated, i.e., diminished irritant receptor sensitivity and increased airway mucus production.

Linn et al. (1982b) also studied the persistence of the attenuation of pulmonary responses that occurs with repeated daily exposures to O_3. Initially, 11 selected subjects, known to have previously exhibited pulmonary decrements in response to O_3 exposure, were exposed for 2 hr daily for four consecutive days to 921 $\mu g/m^3$ (0.47 ppm) O_3. Exposure consisted of alternating 15-min periods of moderate exercise ($\dot{V}_E$ = 3 x resting $\dot{V}_E$) and rest. An exposure to filtered air, under otherwise equivalent conditions, was conducted on the day prior to the first O_3 exposure. The pattern of change in pulmonary response to O_3 was similar to that previously reported for repeated daily exposures. For example, while the initial exposure to filtered air produced essentially no change, on the first O_3 exposure day FEV_1 decreased 11 percent,

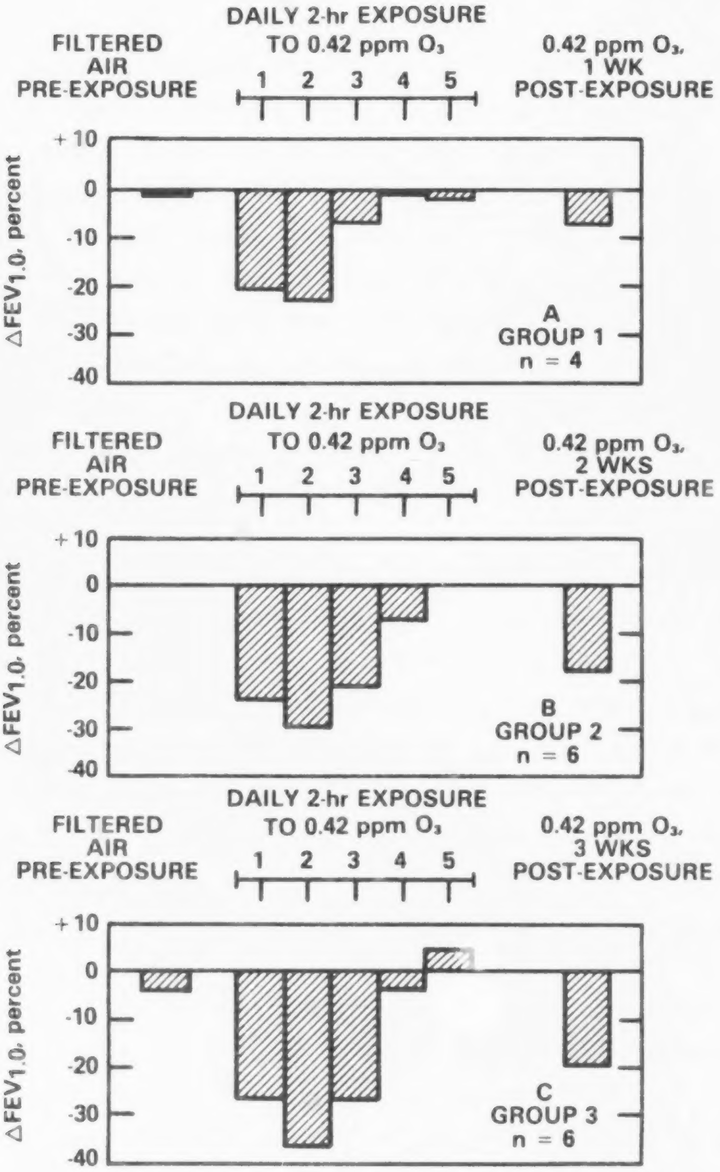

Figure 10-4. Percent change (pre-post) in 1-sec forced expiratory volume ($FEV_{1.0}$), as the result of a 2-hr exposure to 0.42 ppm ozone. Subjects were exposed to filtered air, to ozone for five consecutive days, and exposed to ozone again: (A) 1 wk later; (B) 2 wks later; and (C) 3 wks later.

Source: Horvath et al. (1981).

with a further decline to 23 percent on the second day, returning to approximately 11 percent on the third day. By the fourth day, the mean response was essentially equivalent to that observed with exposure to filtered air. While most of the subjects demonstrated attenuation of response (complete data sets on only seven subjects), the response of one subject, who may have had a persistent low-grade respiratory infection, never diminished. Two others showed relatively little response to the initial daily exposures, but showed some severe responses during follow-up exposures. This pattern was not to be unexpected, based on other studies demonstrating similar atypical responses. To evaluate persistence of attenuated response, subjects repeated O_3 exposures under the above conditions 4 days after the repeated daily exposures and thereafter at 7-day intervals for five successive weeks. Four days after the repeated daily exposures, decrements in pulmonary function in response to O_3 exposure were not significantly different from the first exposure ($FEV_{1.0}$ decreased 11.4 percent on the first day and decreased 8.6 percent four days after the repeated exposures). The decrement in $FEV_{1.0}$ on the subsequent weekly O_3 exposures averaged 13.5 percent. Subjective symptoms generally paralleled lung-function studies, but were significantly fewer on the O_3 exposure which occurred four days after the repeated exposures. Since attenuation of pulmonary responses to O_3 may fail to develop or may be reversed quickly in the absence of frequent exposure, these authors questioned the importance of attenuation of response in the public health sense.

Following the design of an earlier protocol (Farrell et al., 1979), Kulle et al. (1982b) exposed 24 subjects (13 men and 11 women) for 3 hr on five consecutive days beginning on Monday to filtered air during week 1 and to 784 $\mu g/m^3$ (0.4 ppm) of O_3 during week 2. During week 3, they exposed 11 subjects to filtered air on the first day and to 784 $\mu g/m^3$ (0.4 ppm) of O_3 on the second day, while they exposed the remaining 13 subjects for 4 days to filtered air and then to 784 $\mu g/m^3$ (0.4 ppm) of O_3 on the fifth day. One hour prior to the end of each exposure, the subjects performed 15 min of exercise at 100 W ($\dot{V}_E$ = 4 to 5 times resting $\dot{V}_E$). Although the magnitude of decrement was notably less, the patterns of change in responses of FVC and FEV_1 were similar to those observed in previous studies, i.e., attenuation of response occurred during the 5 days of exposure. Attenuation of response was partially reversed 4 days after and not present 7 days after repeated daily exposures. These results agree with those of Linn et al. (1982b), but contrast to those of

Horvath et al. (1981). Since the magnitude of decrements in pulmonary function (and also effective-exposure dose) was notably less in this study than in that of Horvath et al. (1981), these authors have suggested that the duration of attenuation of pulmonary response to O_3 may be related to the magnitude of decrement in response observed with the initial exposure to O_3.

Gliner et al. (1983) performed a study to determine whether daily repeated exposures to a low concentration of O_3 (392 µg/m^3; 0.20 ppm) would attenuate pulmonary function decrements resulting from exposure to a higher O_3 concentration (823 or 980 µg/m^3; 0.42 or 0.50 ppm). Twenty-one subjects (8 male, 13 female) were exposed for 2 hr on five consecutive days to filtered air (0.0 ppm O_3) on day 1, to 392 µg/m^3 (0.20 ppm) of O_3 on days 2, 3, and 4, and to 823 or 980 µg/m^3 (0.42 or 0.50 ppm) of O_3 on day 5. For comparison, subjects who were exposed to 0.42 or 0.50 ppm of O_3 were exposed to the same O_3 concentration under identical conditions 12 weeks prior to or 6 to 8 weeks following the daily repeated exposures. During exposure, subjects alternately rested for 15 min and exercised for 15 min. Minute ventilation was 30 L/min for men and 18 L/min for women. Forced expiratory spirometry (FVC) was performed before and 5 min after the last exercise period. Analysis of continued results from all subjects indicated that three consecutive daily exposures to a low O_3 concentration (392 µg/m^3; 0.20 ppm) did not alter expected pulmonary function response to a subsequent exposure to a higher O_3 concentration (823 or 980 µg/m^3; 0.42 or 0.50 ppm).

Subjects were divided into two groups based on the magnitude of their response to the acute exposure to 823 or 980 µg/m^3 (0.42 or 0.50 ppm) O_3. Nine subjects were considered to be responsive (FEV_1 decrements averaged 34 percent), and nine subjects were considered to be nonresponsive (FEV_1 decrements averaged less than 10 percent). Statistical analysis based on this grouping indicated that responsive subjects exhibited pulmonary function decrements after both their first and second, but not their third, exposure to 392 µg/m^3 (0.20 ppm); decreases in FVC and FEV_1 were about 9 percent. No significant effects of 392-µg/m^3 (0.20-ppm) O_3 exposure were found in the nonresponsive group. In both groups, repeated exposures to 0.20 ppm of O_3 had no influence on the subsequent response to the higher ambient O_3 exposure (823 or 980 µg/m^3; 0.42 or 0.50 ppm). Note that repeated exposures to the low O_3 concentration for only three consecutive days may have constituted insufficient total exposure (some combination of number of exposures, duration of exposures,

$\dot{V}_E$, and O_3 concentration) to affect pulmonary function decrements resulting from exposure to higher O_3 concentrations. Additional studies, with consideration of total exposure and component variables, are needed to clarify this issue.

Haak et al. (1984) made a similar observation as Gliner et al. (1983) that exposure to a low effective dose of O_3 did not attenuate the response to a subsequent exposure at a higher effective dose of O_3. The pattern of pulmonary function decrements was evaluated following repeated daily 4-hr exposures to 784 $\mu g/m^3$ (0.40 ppm) of O_3 with two 15 min periods of heavy exercise ($\dot{V}_E$ = 57 L/min). As expected, pulmonary function decrements were greater on the second of five consecutive days of O_3 exposure; thereafter, the response was attenuated. Exposure at rest to 784 $\mu g/m^3$ (0.4 ppm) of O_3 for two consecutive days had no effect on pulmonary function. Ozone exposure on the next two succeeding days with heavy exercise produced pulmonary function decrements similar to those observed previously in this study for the first two days of exposure to ozone.

Kulle et al. (1984) studied 20 smokers with chronic bronchitis over a 3-week period. The subjects breathed filtered air for 3 hr/day on Thursday and Friday of week 1 (control days), were exposed to 804 $\mu g/m^3$ (0.41 ppm) O_3 for 3 hr/day on Monday through Friday of week 2, and on week 3 breathed filtered air on Monday, then were re-exposed to 0.41 ppm O_3 on Tuesday. Bicycle ergometer exercise was performed at 2 hr of exposure at an intensity of 100 W for 15 min ($\dot{V}_E \sim$ 4-5 times resting). Spirometric measurements and recording of symptoms were made at the completion of all exposures. Small but significant decrements in FVC (2.6 percent) and FEV_3 (3.0 percent) occurred on the first day only of the 5-day repeated exposures as well as on re-exposure 4 days following cessation of the sequential exposures. Symptoms experienced were mild and did not predominate on any exposure days. These results indicate that individuals with chronic bronchitis also have attenuated responses with repeated exposures to O_3 that persist for no longer than 4 days. These results for smokers with chronic bronchitis contrast to those reported by the same investigators for normal nonsmoking subjects exposed under nearly identical conditions (Kulle et al., 1982b). Their normal subjects demonstrated larger decrements in FVC (8 percent) after the first and second exposures; thereafter the response was attenuated. This attenuation of response persisted beyond 4 days, and only with re-exposure 7 days after repeated exposures did significant decreases in

FVC once again appear. These data also support the contention that persistence of an attenuated pulmonary response to O_3 is related to the magnitude of the initial response.

Bedi et al. (1985) performed a study to determine if lung responsiveness to ozone after an initial exposure would persist for 48 hr. Six healthy, nonsmoking audlts (5 females and 1 male) were exposed for 2 hr to filtered air on the first day, to 882 $\mu g/m^3$ (0.45 ppm) O_3 on the second day (day 1), and two days later to a second exposure to 0.45 ppm O_3 (day 2). Subjects alternately rested and exercised at a $\dot{V}_E$ of 27 L/min for 20-min periods. Forced expiratory spirometry was performed before the exposure started and 5 min after each exercise period. There were significant pulmonary function decrements on both O_3 exposure days. The decrements in FVC (DAY 1 = 9.7 percent; DAY 2 = 15.7 percent), FEV_1 (DAY 1 = 13.3 percent; DAY 2 = 22.8 percent), and $FEF_{25-75\%}$ (DAY 1 = 19.6 percent; DAY 2 = 30.4 percent) were 6.0, 9.5, and 10.8 percent larger, respectively, after the day 2 exposure than after the day 1 exposure. Increased pulmonary responsiveness to O_3 was, therefore, still present when exposures were separated by 48 hr. It is not known, however, if this pattern of every-other-day exposures would lead to attenuation of the response, as has been demonstrated for consecutive days of exposure.

Folinsbee and Horvath (1986) studied the time course of hyperresponsiveness following acute ozone exposure. Four groups of healthy, nonsmoking adults (n=6,6,7,7) were exposed for 1 hr to 490 $\mu g/m^3$ (0.25 ppm) O_3 and then reexposed at 12, 24, 48, or 72 hr, respectively. Subjects exercised continuously at a $\dot{V}_E$ of 63 L/min during exposure. Forced expiratory spirometry and maximal voluntary ventilation were performed prior to and within 10 min after exposure. As expected, O_3 exposure was associated with a significant decline in FVC, FEV_1, $FEF_{25-75\%}$, $FEF_{75-85\%}$, MVV, and IC. The general pattern for pulmonary function showed an increased responsiveness to O_3 on the second exposure if it occurred within 24 hr. For example, the decrements in FEV_1 were 6 percent larger in the 12-hr group (EXP 1 = 13 percent; EXP 2 = 19 percent) and 14 percent larger in the 24-hr group (EXP 1 = 20 percent; EXP 2 = 34 percent). An increased responsiveness to O_3 persisted in some subjects for 48 hr but it appeared to be lost within 72 hr. Symptoms generally paralleled the changes in lung function. Differences in persistence of responsiveness to O_3 between the Folinsbee and Horvath (1986) and Bedi et al. (1985) studies are likely related to the different O_3 concentrations used and the magnitude of the initial O_3-induced decrements in lung function.

To determine if nonspecific bronchial reactivity is a factor involved in the attenuation of pulmonary responses to O_3, Dimeo et al. (1981) evaluated the effects of single and sequential O_3 exposures on the bronchomotor response to histamine. To determine the lowest concentration of O_3 that causes an increase in bronchial reactivity to histamine and to determine whether adaptation to this effect of O_3 develops with repeated exposures, they studied 19 healthy, nonsmoking normal adult subjects. Bronchial reactivity was assessed by measuring the rise in specific airway resistance (ΔSR_{aw}) produced by inhalation of 10 breaths of histamine aerosol (1.6-percent solution). In five subjects, bronchial reactivity was determined on four consecutive days without exposure to O_3 (group I). In seven other subjects (group II), bronchial reactivity was assessed on two consecutive days; subjects were exposed to 392 $\mu g/m^3$ (0.2 ppm) of O_3 on the third succeeding day and bronchial reactivity was determined after exposure. Seven additional subjects (group III) had bronchial reactivity assessed for two consecutive days and then again on the next three consecutive days after 2-hr exposures to 784 $\mu g/m^3$ (0.4 ppm) of O_3. Exposures consisted of alternating 15-min periods of rest and light exercise ($\dot{V}_E$ = 2x resting $\dot{V}_E$). Pre-exposure bronchial reactivity of the groups was the same, and no change in bronchial reactivity occurred in group I tested repeatedly but not exposed to O_3. An increase in ΔSR_{aw} provoked by histamine was noted after the first exposure to 784 $\mu g/m^3$ (0.4 ppm) but not to 392 $\mu g/m^3$ (0.2 ppm) of O_3. With three repeated 2-hr exposures to 0.4 ppm on consecutive days, the ΔSR_{aw} produced by histamine progressively decreased, returning to pre-exposure values after the third exposure. Their results indicated that with intermittent light exercise, the lowest concentration of ozone causing an increase in bronchial reactivity in healthy human subjects was between 392 and 784 $\mu g/m^3$ (0.2 and 0.4 ppm), and that attenuation of this effect of O_3 developed with repeated exposures. The lowest concentration of O_3 (identified in other studies using light or moderate exercise) that caused changes in symptoms, lung volumes, or airway resistance was also between 392 and 784 $\mu g/m^3$ (0.2 and 0.4 ppm), and the time course for the development of attenuation of these responses to O_3 was similar to that observed in this study. These authors propose that the appearance of symptoms, changes in pulmonary function, and the increase in bronchial reactivity may be related and caused by a change in the activity of afferent nerve endings in the airway epithelium.

Kulle et al. (1982b) also evaluated the effects of sequential O_3 exposure on bronchial reactivity. Nonsmoking subjects (n = 24) were exposed for 3 hr on five consecutive days each week to filtered air during week 1 and to 784 $\mu g/m^3$ (0.4 ppm) O_3 during week 2. During week 3, they exposed 11 subjects to filtered air on the first day and to 784 $\mu g/m^3$ (0.4 ppm) O_3 on the second day, while they exposed the remaining 13 subjects for 4 days to filtered air and then to 784 $\mu g/m^3$ (0.4 ppm) O_3 on the fifth day. A 15-min period of exercise at 100 W ($\dot{V}_E$ = 4 to 5 times resting $\dot{V}_E$) was performed 1 hr prior to the end of each exposure. After each exposure, a provocative bronchial challenge test was performed to determine bronchial reactivity to methacholine, defined as the log of the methacholine dose that provoked a 35 percent decrease in SG_{aw} from control. Bronchial reactivity to methacholine observed after exposure to O_3 on the initial 2 to 3 days was significantly increased over that observed after exposure to filtered air. On the fourth and fifth consecutive days of O_3 exposure and with reexposure 7 days later, bronchial reactivity to methacholine was not significantly changed. The duration of the attenuated bronchial reactivity response was therefore much longer than that observed for FVC and $FEV_{1.0}$ in the same subjects, as noted earlier in this section.

An issue that merits attention is whether attenuated pulmonary responsiveness is beneficial or detrimental in that it may reflect the presence or development of underlying changes in neural responses or basic injury to lung tissues. Whether the attenuation of pulmonary function responses after repeated chamber exposures to O_3 is suggestive of reduced pulmonary responsiveness for chronically exposed residents of high-oxidant communities also remains unresolved.

10.4 EFFECTS OF OZONE ON VIGILANCE AND EXERCISE PERFORMANCE

Results from animal studies suggest that O_3 causes alterations in motor activity and behavior, but whether these responses result from odor perception, irritation, or a direct effect on the central nervous system (Chapter 9) is unknown. In fact, modification of the inclination to respond was suggested as possibly being more important than changes in the physiological capacity to perform simple or complex tasks. Very few human studies are available to help resolve this issue.

Henschler et al. (1960) determined the olfactory threshold in 10 to 14 male subjects exposed for 30 min to various O_3 concentrations. In a subgroup of 10 subjects, 9 individuals reported detection when the ambient concentration was as low as 39.2 $\mu g/m^3$ (0.02 ppm of O_3). Perception at this low level did not persist, being seldom noted after some 0.5 to 12 min of exposure. The odor of O_3 became more intense at concentrations of 98 $\mu g/m^3$ (0.05 ppm), according to 13 of 14 subjects tested, and it persisted for a longer period of time. No explanation was provided for the olfactory fatigue.

Eglite (1968) studied the effects of low O_3 concentrations on the olfactory threshold and on the electrical activity of the cerebral cortex. He found in his 20 subjects that the minimum perceptible concentration (olfactory threshold) for O_3 was between 0.015 and 0.04 mg/m^3 (0.008 and 0.02 ppm). The few subjects on whom electroencephalograms (EEGs) were recorded showed a 30 to 40 percent reduction of cerebral electrical activity during 3 min of exposure to 0.02 mg/m^3 (0.01 ppm) of O_3. The data are presented inadequately and can be considered only suggestive.

Gliner et al. (1979) determined the effects of 2-hr exposures to 0.0, 490, 980, or 1470 $\mu g/m^3$ (0.0, 0.25, 0.50, or 0.75 ppm) of O_3 on sustained visual and auditory attention tasks (vigilance performance). Eight male and seven female subjects performed tasks consisting of judging and responding to a series of 1-s light pulses which appeared every 3 s. The light pulses were either nonsignals (dimmer) or signals (brighter). When the ratio of signals to nonsignals was low (15 subjects), approximately 1 out of 30 performances was not altered regardless of the ambient level of O_3. However, when the ratio of signals was increased (five subjects), a deficit in performance beyond that of the normal vigilance decline was observed during the 1470-$\mu g/m^3$ (0.75-ppm) O_3 exposure. The results obtained were interpreted within the framework of an arousal hypothesis, suggesting that a high concentration of O_3 may produce overarousal.

Five individuals (four men, one woman) served as subjects (Gliner et al., 1980) in studies designed to evaluate the effects of O_3 on the electrical activity of the brain by monitoring the EEG during psychomotor performance. In the first experiment, a 2-hr visual sustained attention task was unaffected by exposure to filtered air or 1470 $\mu g/m^3$ (0.75 ppm) of O_3. The second experiment involved performing a divided-attention task, which combined a visual choice reaction time situation with an auditory sustained attention task. The

O_3 concentrations were either 0.0, 588, or 1470 μg/m^3 (0.0, 0.3, or 0.75 ppm). Spectral and discriminant function analyses were performed on the EEGs collected during these studies. There was no clear discrimination between O_3 exposure and filtered air using the different parameters obtained from the EEG spectral analysis. Given the inability to obtain a discrimination between clean air and 1470 μg/m^3 (0.75 ppm) of O_3 using these techniques, EEG analysis does not appear to hold any promise as a quantitative method of assessing health effects of low-concentration (i.e., < 1484-μg/m^3; 0.3-ppm) O_3 exposure.

Mihevic et al. (1981) examined the effects of O_3 exposure (0.0, 588, 980 μg/m^3; 0.00, 0.30, and 0.50 ppm) in 14 young subjects who initially rested, then exercised for 40 min at heart rates of 124 to 130 beats/min, and finally rested for an additional 40 min. Pulmonary function measurements (FVC, FEV_1, and MEF_{25-75}) were made during rest periods and after exercise. The primary objective of the study was to examine the effects of exposure during exercise on perception of effort and to evaluate perceptual sensitivity to pulmonary responses. As expected, decrements in FVC, FEV_1, and MEF_{25-75} were significantly greater ($P < 0.01$) immediately after exercise than in the rest condition during either the 588- or 980-μg/m^3 (0.30- or 0.50-ppm) O_3 exposures. The work output remained the same in all conditions. However, the ratings of perceived exertion revealed that the subjects felt they were working harder or making a greater effort when exercising in the 0.50-ppm O_3 condition as compared to in-room air. The increased effort was perceived as a "central" effect (i.e., not related to effort or fatigue in the exercising muscles), which may suggest the perception of increased respiratory effort. The subjects also performed a test of magnitude estimation and production of inspired volume in which they either gave estimates of the percentage of increase in inspiratory capacity or attempted to produce breaths of a given size. From these tests an exponent was derived (by geometric regression analysis), which indicated the "perceptual sensitivity" to change in lung volume. The increase in this exponent following O_3 exposure (588, 980 μg/m^3; 0.30, 0.50 ppm) indicated that the subject's sensitivity to a change in lung volume was greater than it was following filtered-air exposure.

Early epidemiological studies on high school athletes (Chapter 11) provided suggestive information that exercise performance in an oxidant environment is depressed. The reports suggested that the effects may have been related to increased airway resistance or to the associated discomfort in breathing, thus limiting runners' motivation to perform at anticipated high levels. In controlled human studies, exercise performance has been evaluated during short-term maximal exercise or continuous exercise for periods up to 1 hr (Table 10-6). Folinsbee et al. (1977a) observed that maximal aerobic capacity (max $\dot{V}O_2$) decreased 10 percent, maximum attained work load was reduced by 10 percent, maximum ventilation (max $\dot{V}_E$) decreased 16 percent, and maximum heart rate dropped 6 percent after a 2-hr O_3 exposure (1470 μg/m^3; 0.75 ppm) with alternate rest and light exercise. A psychological impact related to the increased pain (difficulty) induced by maximal inspirations may have been the important factor in reduction in performance. Savin and Adams (1979) exposed nine exercising subjects for 30 min to 294 and 588 μg/m^3 (0.15 and 0.30 ppm) O_3 (mouthpiece inhalation). No effects on maximum work rate or max $\dot{V}_{02}$ were found, although a significant reduction in max $\dot{V}_E$ was observed during the 588-μg/m^3 (0.30-ppm) exposure. Similarly, max $\dot{V}_{02}$ was not impaired in men and women after 2-hr exposure and at-rest exposure to 0.0, 980, and 1470 μg/m^3 (0.00, 0.50, and 0.75 ppm) of O_3 (Horvath et al., 1979).

Six well-trained men and one well-trained woman (all except one male being a competitive distance cyclist) exercised continuously on a bicycle ergometer for 1 hr while breathing filtered air or 412 μg/m^3 (0.21 ppm) of O_3 (Folinsbee et al., 1984). They worked at 75 percent max $\dot{V}_{02}$ with mean minute ventilations of 81 L/min. As previously noted (Section 10.2.3), pulmonary function decrements as well as symptoms of laryngeal and/or tracheal irritation, chest soreness, and chest tightness were observed upon taking a deep breath. Anecdotal reports obtained from the cyclists supported the contention that performance may be impaired during competition at similar ambient O_3 levels.

Adams and Schelegle (1983) exposed 10 well-trained distance runners to 0.0, 392, and 686 μg/m^3 (0.0, 0.20, and 0.35 ppm) of O_3 while the runners exercised on a bicycle ergometer at work loads simulating either a 1-hr steady state training bout or a 30-min warmup followed immediately by a 30-min competitive bout. These exercise levels were of sufficient magnitude (68 percent of their max $\dot{V}_{02}$) to increase mean $\dot{V}_E$ to 80 L/min. In the last 30 min of the competitive exercise bout, minute ventilations were approximately 105 L/min. Subjective symptoms increased as a function of O_3 concentration for both continuous and competitive levels. In the competitive exposure, four runners (0.20 ppm) and nine runners (0.35 ppm) indicated that they could not have performed at their maximal levels. Three subjects were unable to complete both the training and competitive simulation exercise bouts at 0.35 ppm O_3, while a

TABLE 10-6. EFFECTS OF OZONE ON EXERCISE PERFORMANCE

Ozone concentration		Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
$\mu g/m^3$	ppm					
294 588	0.15 0.30	UV, NBKI	30 min (mouthpiece) R & CE (8xR) @ progressive work loads to exhaustion	No effect on maximum work rate, anaerobic threshold, or pulmonary function; max $\dot{V}_E$ decreased with 0.30 ppm O_3.	9 male (runners)	Savin and Adams, 1979
392 686	0.20 0.35	UV, UV	1 hr (mouthpiece) IE (77.5) @ variable competitive intervals CE (77.5)	FVC, $FEV_{1.0}$, and FEF_{25-75} decreased, subjective symptoms increased with O_3 concentration at 68% max $\dot{V}O_2$; f_B increased and V_T decreased during CE. No significant O_3 effects on exercise $\dot{V}O_2$, HR, $\dot{V}_E$, or $\dot{V}_A$. No exposure mode effect.	10 male (distance runners)	Adams and Schelegle, 1983
412	0.21	UV, UV	1 hr CE (81)	Decreases in FVC (6.9%), $FEV_{1.0}$ (14.8%), FEF_{25-75}% (18%), IC (11%), and MVV (17%) at 75% max $\dot{V}O_2$. Symptoms reported: laryngeal and tracheal irritation, soreness, and chest tightness on inspiration.	6 male 1 female (distance cyclists)	Folinsbee et al., 1984
490 980 1470	0.25 0.50 0.75	CHEM, NBKI	2 hr R (8) & CE @ progressive work loads to exhaustion	No effect on maximum exercise performance (max $\dot{V}O_2$, HR, and total performance time).	8 male 7 female	Horvath et al., 1979
1470	0.75	MAST, NBKI	2 hr IE (2.5xR) @ 15-min intervals	HR_{max}, $\dot{V}_E$, V_T, $\dot{V}O_{2max}$, and maximum workload all decreased. At maximum workload only, f_R increased (45%) and V_T decreased (29%).	13 male	Folinsbee et al., 1977a

[a] Measurement method: CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry.

[b] Calibration method: NBKI = neutral buffered potassium iodide; UV = UV photometry.

[c] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or as a multiple of resting ventilation.

[d] See Glossary for the definition of symbols.

fourth failed to complete only the competitive ride. As previously noted (Section 10.2.3), the high ventilation volumes resulted in marked pulmonary function impairment and altered ventilatory patterns. The decrements were the result of physiologically induced subjective limitations of performance due to respiratory discomfort. The authors found it necessary to reduce the 68 percent max $\dot{V}_{O2}$ work load by some 20 to 30 percent in two of their subjects for them to complete the final 15 min (of the 30-min work time) in their competitive test.

Although studies on athletes (not all top-quality performers) have suggested some decrement in performance associated with O_3 exposure, too limited a data base is available at this time to provide judgmental decisions concerning the magnitude of such impairment. Subjective statements by individuals engaged in various sport activities indicate that these individuals may voluntarily limit strenuous exercise during high-oxidant concentrations. However, increased ambient temperature and relative humidity are also associated with episodes of high-oxidant concentrations, and these environmental conditions may also enhance subjective symptoms and physiological impairment during O_3 exposure (see Section 10.2.9.3). Therefore, it may be difficult to differentiate any performance effects due to ozone from those due to other conditions in the environment. Several reviews on exercising subjects have appeared in the literature (Horvath, 1981; Folinsbee, 1981; McCafferty, 1981; Folinsbee and Raven, 1984).

10.5 INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS

An important issue is whether or not O_3 interacts with other pollutants to produce additive as well as greater than additive effects beyond those resulting from exposure to O_3 or the other pollutants alone. Also important to determine is whether no interactions occur when several pollutants are present simultaneously. Table 10-7 presents a summary of data on interactions between O_3 and other pollutants.

10.5.1 Ozone Plus Sulfates or Sulfuric Acid

Several studies have addressed the possible interaction between O_3 and sulfur compounds. Bates and Hazucha (1973) and Hazucha and Bates (1975) exposed eight volunteer male subjects to a mixture of 725 $\mu g/m^3$ (0.37 ppm) of

TABLE 10-7. INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS

Ozone concentration µg/m³	Ozone concentration ppm	Pollutant[a]	Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
					A. $O_3 + SO_2$:		
294 393	0.15 0.15	O_3 SO_2	CHEM, NBKI EC	2 hr IE(25) @ 15-min intervals	SG_{aw} decreased; possible synergism is questionable. Statistical approach is weak.	6 male	Kagawa and Tsuru, 1979c
588 2620	0.3 1.0	O_3 SO_2	UV, UV FP	2 hr IE (38); alternating 30-min exercise and 10-min rest periods	FVC, FEV_1, and $FEF_{25-75\%}$ decreased after exposure to O_3 alone; when combined with SO_2, similar but smaller decreases were observed. No additive or synergistic effects were found.	22 male	Folinsbee et al., 1985
725 970	0.37 0.37	O_3 SO_2	MAST, NBKI EC	2 hr IE(2xR) @ 15-min intervals	Decrement in spirometric variables (FVC, MEFR 50%); synergism reported. Interpretation complicated by the probable presence of H_2SO_4.	8 male	Hazucha, 1973 Bates and Hazucha, 1973 Hazucha and Bates, 1975
725 970	0.37 0.37	O_3 SO_2	CHEM, NBKI FP	2 hr IE(2xR) @ 15-min intervals	Decreased forced expiratory function ($FEV_{1.0}$, FVC) relative to O_3 exposure alone in combined group of normal and sensitive L.A. subjects; more severe symptoms and greater decrement of $FEV_{1.0}$ in Montreal (5.2%) than L.A. sensitive (3.7%) subjects.	4 normal (L.A) 5 sensitive (L.A.) 4 normal (Montreal)	Bell et al., 1977
725 970 100	0.37 0.37	O_3 SO_2 H_2SO_4	UV, NBKI FP IC	2 hr IE(2xR) @ 15-min intervals	Small decreases in pulmonary function (FVC, $FEV_{1,2,3}$, MMFR, $\dot{V}_{max50}$, $\dot{V}_{max25}$) and slight increase in symptoms due primarily to O_3 alone; H_2SO_4 was 93% neutralized.	19 male	Kleinman et al., 1981
784 1048	0.4 0.4	O_3 SO_2	CHEM, NBKI FP	2 hr IE(30) @ 15-min intervals	Decreased forced expiratory function (FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, $FEF_{50\%}$) following exposure to either O_3 or $O_3 + SO_2$; no differences observed between O_3 alone and $O_3 + SO_2$.	9 male	Bedi et al., 1979
784 1048	0.4 0.4	O_3 SO_2	CHEM, NBKI FP	2 hr IE(30) @ 15-min intervals	Observed decrement in pulmonary function ($FEV_{1.0}$, FVC, $FEF_{25-75\%}$, $FEF_{50\%}$, ERV, TLC) and increase in symptoms reflected changes due to O_3; no synergism was found.	8 male	Bedi et al., 1982
					B. $O_3 + H_2SO_4$:		
294 200	0.15	O_3 H_2SO_4	CHEM, NBKI IC	2 hr IE @15-min intervals	SGaw decreased; no interaction reported. Questionable statistics.	7 male	Kagawa, 1983a

TABLE 10-7 (continued). INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS

Ozone concentration		Pollutant[a]	Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
µg/m³	ppm						
588 100	0.3	O_3 H_2SO_4	MAST, NBKI & CHEM, NBKI TS	2 hr IE(35) for 15 min 4 hr IE(35) for 15 min	No significant O_3-related changes in pulmonary function or bronchial reactivity to methacholine. Bronchial reactivity decreased following a 4-hr exposure to H_2SO_4.	7 male 5 female	Kulle et al., 1982a
784 100 133 116 80	0.4	O_3 H_2SO_4 $(NH_4)_2SO_4$ NH_4HSO_4 NH_4NO_3	CHEM, NBKI	2-4 hr IE for two 15-min periods	Decrement in pulmonary function due to O_3 alone; more apparent after 4 hr than 2 hr; no interaction; recovery within 24 hr.	124 male (divided into 10 exposure groups)	Stacy et al., 1983
					C. O_3 + CO:		
588 115000	0.3 100.0	O_3 CO	MAST, BAKI IR	1 hr (mouthpiece) CE (51 for male and 34.7 for female subjects).	Decrement in pulmonary function due to O_3 alone: FVC, $FEV_{1.0}$ and $FEF_{25-75\%}$ decreased; f_B increased and V_T decreased with exercise.	12 male 12 female (equally divided by smoking history)	DeLucia et al., 1983
					D. O_3 + NO_2:		
196 9400	0.1 5.0	O_3 NO_2	CHEM, NBKI MAST (NO_2)	2 hr IE(2xR) @ 15-min intervals	Decreases in PaO_2 and increases in Raw due predominantly to NO_2 alone. No interaction reported.	12 male	von Nieding et al., 1977 von Nieding et al., 1979
294 280	0.15 0.15	O_3 NO_2	MAST, NBKI and CHEM, NBKI MAST, (NO_2) and CHEM, C	2 hr IE(25) @ 15-min intervals	SGaw decreased in 5/6 subjects during O_3 exposure, 3/6 subjects during NO_2 exposure, and in all subjects during the combined exposure. More than additive effect reported in 3/6 subjects. Coughing, chest pains, and chest discomfort related to O_3 exposure.	6 male	Kagawa and Tsuru, 1979b
490-980 560 35000	0.25-0.5 0.3 30.0	O_3 NO_2 CO	CHEM, NBKI CHEM, C IR	2-4 hr R & IE(2xR) @15-min intervals	No interaction reported. Changes observed in spirometry, lung mechanics, and small airway function in non-reactors (IE) and hyperreactors (R) at 0.5 ppm O_3.	16 normal and reactive subjects	Hackney et al., 1975a,b,c
980 940	0.5 0.5	O NO_2	CHEM, NBKI CHEM, C	2 hr IE (40) for 30 min	Decreases in FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, and $FEF_{50\%}$; ventilatory and metabolic variables were not changed; response was similar to that observed in O_3 exposure alone. Tightness in the chest and difficulty taking deep a breath was reported along with cough, substernal soreness, and shortness of breath.	8 male	Folinsbee et al., 1981

TABLE 10-7 (continued). INTERACTIONS BETWEEN OZONE AND OTHER POLLUTANTS

Ozone concentration μg/m³	Ozone concentration ppm	Pollutant[a]	Measurement[b,c] method	Exposure duration and activity[d]	Observed effect(s)[e]	No. and sex of subjects	Reference
980- 1372 940 1320	0.5- 0.7 0.5- 0.7	O_3 NO_2	MAST, NBKI and CHEM, NBKI MAST (NO_2) and CHEM, C	1 hr (mouthpiece) R	No significant changes in SGaw, $\dot{V}$max 50%, or $\dot{V}$max 25%.	5 male	Toyama et al., 1981
					E. $O_3 + NO_2 + SO_2$:		
49- 196 100- 9000 314 13000	0.025- 0.1 0.06- 5.0 0.12- 5.0	O_3 NO_2 SO_2	CHEM, NBKI MAST (NO_2) TS	2 hr IE (2xR) @ 15-min intervals	Decreases in PaO_2 and increases in Raw due to NO_2 alone at maximum concentrations; no effect at minimum concentrations. No interaction reported.	11 male	von Nieding et al., 1979
157 300 900	0.08 0.16 0.34	O_3 NO_2 SO_2	CHEM, NBKI and GS, CHEM CHEM, C	8 hr R	No effect on lung function, blood gases, or blood chemistry; questionable statistics.	15 male	Islam and Ulmer, 1979b
196 9400 13100	0.1 5.0 5.0	O_3 NO_2 SO_2	CHEM, NBKI GS, CHEM CHEM, C	2 hr IE	Random effects reported; questionable statistics; unknown exercise level.	24 male (divided into 3 age groups)	Islam and Ulmer, 1979a
294 280 393	0.15 0.15 0.15	O_3 NO_2 SO_2	CHEM, NBKI CHEM, C EC	2 hr IE @ 15-min intervals	Decreases in SG_{aw} due to O_3 alone. No interaction reported. Questionable statistics.	7 male	Kagawa, 1983a, 1983b

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[a] Pollutants studied for interactive effects: 0 = ozone; SO = sulfur dioxide; H_2SO_4 = sulfuric acid; $(NH_4)_2SO_4$ = ammonium sulfate; NH_4HSO_4 = ammonium bisulfate; NH_4NO_3 = ammonium nitrate; CO = carbon monoxide; NO_2 = nitrogen dioxide.

[b] Measurement method: MAST = KI-Coulometric (Mast meter); MAST (NO_2) = microcoulometric NO_2 analyzer; CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry; GS-CHEM = gas solid chemiluminescence; IC = ion chromatography; EC = electrical conductivity SO_2 analyzer; FP = flame photometry SO_2 analyzer; TS = total sulfur analyzer; IR = infrared CO analyzer.

[c] Calibration method: NBKI = neutral buffered potassium iodide; BAKI = boric acid potassium iodide; C = colorimetric (Saltzman).

[d] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or as a multiple of resting $\dot{V}_E$.

[e] See Glossary for the definition of symbols.

[f] Part of a larger study of 231 subjects.

O_3 and 0.37 ppm of sulfur dioxide (SO_2) for 2 hr. Temperature, humidity, concentrations, and particle sizes of ambient aerosols (if any) were not measured. Sulfur dioxide alone had no detectable effect on lung function, while exposure to O_3 alone resulted in decrements in pulmonary function. The combination of gases resulted in more severe respiratory symptoms and pulmonary changes than did O_3 alone. Using the maximal expiratory flow rate at 50 percent vital capacity as the most sensitive indicator, no change occurred after 2 hr of exposure to 0.37 ppm SO_2 alone. However, during exposure to 725 $\mu g/m^3$ (0.37 ppm) O_3 a 13 percent reduction occurred, while exposure to the mixture of 725 $\mu g/m^3$ (0.37 ppm) O_3 and 0.37 ppm SO_2 resulted in a reduction of 37 percent in this measure of pulmonary function. The effects resulting from O_3 and SO_2 in combination appeared in 30 min, in contrast to a 2-hr time lag for exposure to O_3 alone.

Bell et al. (1977) attempted to corroborate these studies using four normal and four O_3-sensitive subjects. They showed that the O_3 + SO_2 mixture had an overall greater effect on pulmonary function measures than did O_3 alone. Differences ranging from 1.2 percent for FVC to 16.8 percent for $\dot{V}_{25}$ were detected during O_3 + SO_2 exposure relative to O_3 exposure alone in normal subjects. The mean $FEV_{1.0}$ decreased 4.7 percent after O_3 + SO_2 exposure relative to O_3 alone in the sensitive subjects. When normals and sensitives were combined, the mean $FEV_{1.0}$ and FVC were both significantly lower after the O_3 + SO_2 exposure. Four of the Hazucha and Bates (1975) study subjects were also studied by Bell et al. (1977). Two of these subjects had unusually large decrements in FVC (40 percent) and FEV_1 (44 percent) in the first study (Bates and Hazucha, 1973), while the other two had small but statistically significant decrements. None of the subjects responded in a similar manner in the Bell et al. (1977) study.

To determine why some of the Montreal subjects were less reactive to the SO_2-O_3 mixture when studied in Los Angeles compared to Montreal, Bell et al. (1977) compared exposure dynamics in the two chambers. Analysis of the design of the Montreal chamber and pollutant delivery system indicated that concentrated streams of SO_2 and O_3 could have reacted rapidly with each other and with ambient impurities like olefins, to form a large number of sulfuric acid (H_2SO_4) nuclei which grew by homogeneous condensation, coagulation, and absorption of ammonia (NH_3) during their 2-min average residence time in the chamber. A retrospective sampling of the aerosol composition used for the original SO_2-O_3 study in Montreal (Hazucha and Bates, 1975) using particle samplers and chemical analysis in the chamber showed that acid sulfate particles could have been 10- to 100-fold higher (100 to 200 $\mu g/m^3$), and thus might have been responsible for the synergistic effects observed. However, recent studies conducted by Kleinman et al. (1981) involving identical concentrations of SO_2 and O_3 showed that the presence of 100 $\mu g/m^3$ H_2SO_4 did not alter the response obtained with the SO_2-O_3 mixture alone. (See later discussion in this section.)

Bedi et al. (1979) exposed nine young healthy nonsmoking men (18 to 27 years old) to 784 $\mu g/m^3$ (0.4 ppm) O_3 and 0.4 ppm SO_2 singly and in combination for 2 hr in an inhalation chamber at 25°C and 45 percent rh. The subjects exercised intermittently for one-half of the exposure period. Pulmonary function was measured before, during, and after the exposure. Subjects exposed to filtered air or to 0.4 ppm SO_2 showed no significant changes in pulmonary function. When exposed to either O_3 or O_3 plus SO_2, the subjects showed statistically significant decreases in maximum expiratory flow ($FEV_{1.0}$, $FEF_{25-75\%}$, and $FEF_{50\%}$) and FVC. There were no significant differences between the effects of O_3 alone and the combination of O_3 + SO_2; thus, no synergistic effects were discernible in their subjects. Although particulate matter was not present in the inlet air, whether particles developed in the chamber at a later point is not known.

Chamber studies were also conducted by Kagawa and Tsuru (1979c), who exposed six subjects for 2 hr with intermittent exercise (50 W; i.e., ventilation of 25 L/min) for periods of 15 min of exercise separated by periods of 15 min of rest. The exposures were performed weekly in the following sequence: filtered air, 0.15 ppm of O_3; filtered air, 0.15 ppm of SO_2; filtered air; and finally 0.15 ppm of O_3 + 0.15 ppm of SO_2. Pulmonary function measurements were obtained prior to exposure, after 1 hr in the chamber, and after leaving the chamber. Although a number of pulmonary function tests were performed, change in SG_{aw} was used as the most sensitive test of change in function. They reported a significant decrease in five of the six young male subjects exposed to O_3 alone. In three of the subjects, they reported a significantly greater decrease in SG_{aw} after exposure to the combination of pollutants than with O_3 exposure alone. Two other subjects had similar decreases with either O_3 or O_3 + SO_2 exposure. Subjective symptoms of cough and bronchial irritation were reported to occur in subjects exposed to either O_3 or the O_3 + SO_2 combination. The authors suggested that the combined effect of the two gases on SG_{aw} is more than simply additive in some exercising subjects. This conclusion is questionable, however, because of the small number of subjects responding and the use of t-tests of paired observations to test the significance of pollutant-exposure effects. The statistical approach is weak despite the fact that the author selected a significance level of $P < 0.01$. The question of potential synergistic interaction between SO_2 and O_3 therefore remains unresolved by this study.

Bedi et al. (1982) attempted to explain the conflict of opinion over the cause of synergistic effects reported by Hazucha and Bates (1975) and Kagawa and Tsuru (1979c) for humans exposed to the combination of O_3 and SO_2. While intermittently exercising ($\dot{V}_E$ ~30 L/min), eight young adult nonsmoking males were randomly exposed on separate occasions for 2 hr to filtered air, 0.4 ppm SO_2, 748 $\mu g/m^3$ (0.4 ppm) of O_3, and 0.4 ppm of SO_2 plus 784 $\mu g/m^3$ (0.4 ppm) of O_3 at 35°C and 85 percent rh. No functional changes in $FEV_{1.0}$ occurred as a result of exposure to filtered air or 0.4 ppm of SO_2, but decreases in $FEV_{1.0}$ occurred following exposure to either 784 $\mu g/m^3$ (0.4 ppm) of O_3 (6.9 percent) or the combination of 784 $\mu g/m^3$ (0.4 ppm) of O_3 plus 0.4 ppm of SO_2 (7.4 percent). Thoracic gas volume (TGV) increased and $FEF_{50\%}$ decreased in the O_3 exposures, while FVC, $FEF_{25-75\%}$, $FEF_{50\%}$, ERV, and TLC all decreased in the O_3/SO_2 and O_3 exposures. However, no significant differences were found between the O_3 exposure and the O_3 plus SO_2 exposure. In this study, statistical analyses were performed using ANOVA procedures.

An analysis of the data obtained in the 1982 study and a prior study (Bedi et al., 1979) was also made using t-tests to compare data from these two studies with data obtained by Kagawa and Tsuru (1979c), who reported a synergistic effect consequent to exposure to 0.15 ppm of SO_2 and 294 $\mu g/m^3$ (0.15 ppm) of O_3 using t-tests. The experimental designs of the Bedi et al. and the Kagawa and Tsuru studies were essentially similar. Reanalysis of the Bedi et al. data using t-tests and expressing data as relative changes indicated that the SG_{aw} was not altered in the 25°C-45 percent rh environment but decreased 10.6 percent ($P < 0.05$) in the SO_2 exposure and 19 percent ($P < 0.01$) in O_3 plus SO_2 exposure in hot, wet conditions. These investigators concluded that in one sense they confirmed the findings (based on t-tests) of Kagawa and Tsuru, but under different conditions. This might suggest a small potential effect on SG_{aw}. They then stated, "Nonetheless, we believe that the use of a more stringent statistical approach provides for better analysis of collected data and that we are correct in stating that synergism had not occurred."

Folinsbee et al. (1985) exposed 22 healthy nonsmoking men (23.6 ± 8.1 years of age) for 2 hr to a combination of 588 $\mu g/m^3$ (0.3 ppm) O_3 and 1.0 ppm SO_2 as well as to each gas individually. The subjects alternated 30-min periods of treadmill exercise at a ventilation of 38 L/min with 10-min rest periods during the exposure. Forced expiratory maneuvers were performed before exposure and 5 min after each of three exercise periods; MVV, FRC, R_{aw}, and TGV were measured before and after exposure. After O_3 exposure alone, there were significant decreases in FVC, FEV_1, and $FEF_{25-75\%}$. There were no significant changes in pulmonary function after SO_2 exposure alone. Combined exposure to $SO_2 + O_3$ produced similar but smaller changes compared to those found after O_3 exposure alone. These small differences were not in a direction that would support the hypothesis of either a synergistic or additive effect on pulmonary function. In general, there were no important health-related differences between the effects of O_3 alone and $O_3 + SO_2$.

Few studies have been reported in which subjects were exposed to O_3 and H_2SO_4. Kagawa (1983a) summarized some results obtained on seven subjects intermittently resting and exercising during a 2-hr exposure to 294 $\mu g/m^3$ (0.15 ppm) of O_3 and 0.2 mg/m^3 of H_2SO_4. Using t-tests to analyze his data, he reported a highly significant ($P < 0.01$) decrease (10.2 percent) in SG_{aw}. However, not enough details are provided to allow adequate analysis.

Kleinman et al. (1981) conducted studies in which 19 volunteers with normal pulmonary function and no history of asthma were exposed on two separate days to clean air and to an atmospheric mixture containing O_3 (725 $\mu g/m^3$, 0.37 ppm), SO_2 (0.37 ppm), and H_2SO_4 aerosol (100 $\mu g/m^3$, MMAD = 0.5 μm; $\sigma_g = 3.0$). Chemical speciation data indicated that 93 percent of the H_2SO_4 aerosol had been partially neutralized to ammonium bisulfate. Additional data suggested that the acidity of the aerosol in the chamber decreased as a function of time during exposure, so that at the beginning of the exposures subjects were exposed to higher concentrations of H_2SO_4 than they were at the end of exposures. During this 2-hr period, the subjects alternately exercised for 15 min, at a level calibrated to double minute ventilation, and rested for 15 min. Statistical analysis of the group average data suggested that the mixture may have been slightly more irritating to the subjects than O_3 alone. A large percentage (13 of 19) of the subjects exhibited small decrements in pulmonary function following exposure to the mixture. The group average $FEV_{1.0}$ on the exposure day was depressed by 3.7 percent of the control value. However, the magnitudes of the $FEV_{1.0}$ changes were not higher than those observed in subjects exposed to O_3 alone (expected decreases of 2.8 percent). The authors concluded that the presence of H_2SO_4 aerosols did not substantially alter the irritability resulting from O_3-SO_2.

Stacy et al. (1983) studied 234 healthy men (18 to 40 years old) exposed for 4 hr to air, O_3, NO_2, or SO_2; to H_2SO_4, ammonium sulfate [$(NH_4)_2SO_4$], ammonium bisulfate (NH_4HSO_4), or ammonium nitrate (NH_4NO_3) aerosols; or to mixtures of these gaseous and aerosol pollutants. The subjects were divided into 20 groups so that each group contained 9 to 15 subjects. The exposure groups of interest were filtered air ($n = 10$); 784 $\mu g/m^3$ (0.4 ppm) of O_3 ($n = 12$); 100 $\mu g/m^3$ of H_2SO_4 ($n = 11$); 133 $\mu g/m^3$ of $(NH_4)_2SO_4$ ($n = 13$); 116 $\mu g/m^3$ of NH_4HSO_4 ($n = 15$); 80 $\mu g/m^3$ of NH_4NO_3 ($n = 12$); and the mixtures $O_3 + H_2SO_4$ ($n = 13$), $O_3 + (NH_4)_2SO_4$ ($n = 15$), $O_3 + NH_4HSO_4$ ($n = 11$), and $O_3 + NH_4NO_3$ ($n = 12$). Ambient conditions were 30°C db, 85 percent rh because of the need to maintain the aerosol particles in proper suspension. Two 15-min bouts of treadmill exercise were performed, one beginning at 100 min into the exposure and the second beginning at 220 min. Minute ventilations were not reported. Pulmonary function was measured during a rest period before exposure, 5 to 6 min following the termination of the exercise, and 24 hr later. Data were analyzed by multivariate analyses of variance. Airway resistance, lung volume, and flow rates showed a statistically significant effect of the gaseous pollutant (O_3) with greater changes reported at 4 hr than at 2 hr of exposure. None of the particulates significantly altered pulmonary functions compared with the filtered-air exposure, and there was no indication of interaction between O_3 and the particulates. Exposure to O_3 alone and with particles was also associated with symptoms of irritation, such as shortness of breath, coughing, and minor throat irritation. At 24 hr post-exposure, all pulmonary values had returned to pre-exposure levels.

Kulle et al. (1982a) studied the responses of 12 healthy nonsmokers (seven men, five women) exposed to O_3 and H_2SO_4 aerosols. Ozone concentrations were 588 $\mu g/m^3$ (0.3 ppm) and H_2SO_4 aerosol levels were 100 $\mu g/m^3$ (MMAD = 0.13 μm; $\sigma_g = 2.4$). These studies were conducted over a 3-week period; a 2-hr exposure to O_3 during the first week, a 4-hr exposure to H_2SO_4 during the second week, and a 2-hr exposure to O_3 followed by a 4-hr exposure to H_2SO_4 during the third week. The protocol followed in each of these weekly exposure regimes was day 1 - filtered air, day 2 - pollutant, and day 3 - filtered air. A methacholine aerosol challenge was made at the completion of each exposure day. Subjects were exercised for 15 min 1 hr prior to the completion of the exposure. The work load was 100 W at 60 rpm, with an assumed $\dot{V}_E$ of approximately 30 to 35 L. No discernible risk was apparent as a consequence of exposing the nonsmoking healthy young adults to O_3 followed by respirable H_2SO_4 aerosol. Bronchial reactivity decreased with H_2SO_4 aerosol exposure at a statistical level approaching significance ($0.05 < p < 0.10$). Pulmonary function changes (SG_{aw}, FVC, FEV_1, FEV_3, and bronchial reactivity to methacholine) following the O_3 exposure were not significant. However, some subjects did report typical symptoms observed in other O_3 exposures.

10.5.2 Ozone and Carbon Monoxide

DeLucia et al. (1983) reported the only study in which subjects were exposed to carbon monoxide (CO) and O_3. Subjects exercised at 50 percent max $\dot{V}_{O2}$ for 1 hr in the following ambient conditions: filtered air, 100 ppm of CO, 588 $\mu g/m^3$ (0.30 ppm) of O_3, and 100 ppm of CO plus 588 $\mu g/m^3$ (0.30 ppm) of O_3. These gas mixtures were administered directly, the subjects inhaling them orally for the entire exposure period. Twelve nonsmokers, six men and six women, and 12 smokers (not categorized as to smoking habits), equally divided by sex, served as subjects. There were relatively large differences in fitness between men and women as well as between smokers and nonsmokers, which could be responsible for some of the differences reported. Cardiorespiratory performance, heart rate, oxygen uptake, and minute ventilation were not substantially higher during exercise bouts where O_3 was present. All subjects exercised at 50 percent max $\dot{V}_{O2}$, equivalent to a mean $\dot{V}_E$ of 45.0 to 51.8 L/min for the men and 29.7 to 36.8 L/min for the women. The women, therefore, probably inhaled less O_3 than the men. Carboxyhemoglobin (COHb) levels attained at the end of the exercise period were similar for the two sexes, an average increase of 5.8 percent. Smokers' final COHb values were 9.3 ± 1.2 percent, compared with nonsmokers' levels of 7.3 ± 0.8 percent.

Based on the limited data available, exposure to CO and O_3 does not appear to result in any interactions. The effects noted appear to be related primarily to O_3.

10.5.3 Ozone and Nitrogen Dioxide

Studies describing the responses of subjects to the combination of these two pollutants are summarized in Table 10-7. Hackney et al. (1975a,b,c) and von Nieding et al. (1977, 1979) noted that no interactions were observed and that the pulmonary function changes were due to O_3 alone for the concentrations present. Kagawa and Tsuru (1979b) evaluated the reactions of six subjects (one smoker) to 294 $\mu g/m^3$ (0.15 ppm) O_3 and 0.15 ppm NO_2, singly and in combination. They used the standard exposure time of 2 hr with alternating 15-min periods of rest and exercise at 50 W. SG_{aw} was determined prior to flow volume measurements and prior to and at two intervals during the exposure period. A fixed sequence of pollutant exposures was followed at weekly intervals, i.e., filtered air, 294 $\mu g/m^3$ (0.15 ppm) of O_3, filtered air, 0.15 ppm of NO_2, filtered air, 0.15 ppm (O_3 + NO_2), and filtered air. Statistical analyses were by t-tests. Subjective symptoms were reported in some subjects only when O_3 was present. Significant decreases in SG_{aw} occurred in five of six subjects exposed to O_3, three of six subjects exposed to NO_2, and six of six subjects exposed to O_3 + NO_2.

Kagawa (1983a) briefly reported that under the conditions of his exposure (2 hr to 0.15 ppm O_3 + 0.15 ppm NO_2) SG_{aw}, $\dot{V}_{50\%}$, and VC decreased. However, no significant differences were observed between O_3 alone and the combination of O_3 + NO_2. Subjective symptoms were equivalent in both O_3 exposures.

Five subjects sitting in a body plethysmograph inhaled orally either filtered air, 0.7 ppm of NO_2, 1372 $\mu g/m^3$ (0.7 ppm) of O_3, or 0.5 ppm of O_3 + 0.5 ppm of NO_2 for 1 hr (Toyama et al., 1981). Specific airway conductance and isovolume flows ($\dot{V}_{max\ 25\%}$ and $\dot{V}_{max\ 50\%}$) were measured before and at the end of exposure, and 1 hr later. No significant changes were observed for any of the ambient conditions and consequently no interactions could be detected.

Folinsbee et al. (1981) exposed eight healthy men for 2 hr to either filtered air or 980 $\mu g/m^3$ (0.5 ppm) of O_3 plus 0.5 ppm of NO_2 in filtered air under four different environmental conditions: (1) 25°C, 45 percent rh; (2) 30°C, 85 percent rh; (3) 35°C, 40 percent rh; and (4) 40°C, 50 percent rh. Subjects rested for the first hour, exercised at a $\dot{V}_E$ of 40 L/min during the next half hour, and then rested for the final 30 min of exposure. Pulmonary function measurements were made prior to exposure, immediately after the exercise period, and again at the end of the 2-hr period. Significant decreases occurred in FVC, $FEV_{1.0}$, $FEF_{25-75\%}$, and $FEF_{50\%}$ during the O_3-NO_2 exposure. Ventilatory and metabolic variables, expired ventilation, oxygen uptake, tidal volume, and respiratory frequency were unaffected by O_3 and NO_2 exposure. Thermal conditions modified heart rate, ventilation, and FVC. Greater changes in pulmonary functions were seen in both groups following the exercise period with recovery of the decrements toward the pre-exposure value during the succeeding half hour of rest. In this study, no synergism or interaction between O_3 and NO_2 was observed over the entire range of ambient temperatures and relative humidities.

10.5.4 Ozone and Other Mixed Pollutants

Von Nieding et al. (1979) exposed 11 subjects to O_3, NO_2, and SO_2 singly and in various combinations. The subjects were exposed for 2 hr with 1 hr devoted to exercise (intermittent), which doubled their ventilation. The work periods were of 15 min duration alternating with 15-min periods at rest. In the actual exposure experiments, no significant alterations were observed for PO_2, PCO_2, and pH in arterialized capillary blood or in TGV. Arterial oxygen tension (PaO_2) was decreased (7 to 8 torr) by exposure to 5.0 ppm of NO_2 but was not further decreased following exposures to 5.0 ppm of NO_2 and 5.0 ppm of SO_2 or 5.0 ppm of NO_2, 5.0 ppm of SO_2 and 196 $\mu g/m^3$ (0.1 ppm) of O_3 or 5.0 ppm of NO_2 and 196 $\mu g/m^3$ (0.1 ppm) of O_3. Airway resistance increased significantly (0.5 to 1.5 cm $H_2O/L/s$) in the combination experiments to the same extent as in the exposures to NO_2 alone. In the 1-hr post-exposure period of the NO_2, SO_2, and O_3 experiment, R_t continued to increase. Subjects were also exposed to a mixture of 0.06 ppm NO_2, 0.12 ppm of SO_2, and 49 $\mu g/m^3$ (0.025 ppm) of O_3. No changes in any of the measured parameters were observed. These same subjects were challenged with 1-, 2-, and 3-percent aerosolized solutions of ACh following control (filtered-air) exposure and exposure to 5.0-ppm NO_2, 5.0-ppm SO_2, and 0.1-ppm O_3 mixture, as well as after the 0.06-ppm NO_2, 0.12-ppm SO_2, and 49-$\mu g/m^3$ (0.025-ppm) O_3 mixture exposures. Individual pollutant gases were not evaluated separately. ACh challenge caused the expected rise in airway resistance in the control study. Specific airway resistance (R_{aw} x TGV) was significantly greater following the combined pollutant exposures than in the control study.

In another study of simultaneous exposure to SO_2, NO_2, and O_3, three groups of eight subjects, each of different ages (<30, >49, and between 30 to 40 years) were exposed for 2 hr each day in a chamber on three successive days (Islam and Ulmer, 1979a). On the first day, subjects breathed filtered air and exercised intermittently (levels not given); on the second day they were exposed at rest to 5.0 ppm of SO_2, 5.0 ppm of NO_2, and 196 $\mu g/m^3$ (0.1 ppm) of O_3; and on the third day the environment was again 5.0 ppm of SO_2, 5.0 ppm of NO_2, and 196 $\mu g/m^3$ (0.1 ppm) of O_3, but the subjects exercised intermittently during the exposure. Statistical evaluation of data for the 11 lung-function test parameters and two blood gas parameters (PaO_2 and $PaCO_2$) was not reported.

These measurements were made before exposure, immediately post-exposure, and 3 hr post-exposure. Individual variability was quite marked. The investigators concluded that no synergistic effects occurred in their healthy subjects. However, since they did not systematically expose these subjects to the individual components of their mixed pollutant environment, the conclusion can only be justified in that they apparently saw no consistent changes. There were some apparent changes in certain individuals related to exercise (unknown level) and age, but the data were not adequately presented or analyzed.

Islam and Ulmer (1979b) studied 15 young healthy males during chamber exposures to 0.9 mg/m^3 (0.34 ppm) SO_2, 0.3 mg/m^3 (0.16 ppm) NO_2, and 0.15 mg/m^3 (0.08 ppm) O_3. Ten subjects were exposed to 1 day of filtered air and four successive days of the gas mixture. Another group of five subjects was exposed for 4 days to the pollutant mixture followed by 1 day to filtered air. Each exposure lasted 8 hr. Following each exposure, the subjects were challenged by an ACh aerosol. Eight pulmonary function tests and four blood tests (PaO_2, $PaCO_2$, hemoglobin, and lactate dehydrogenase) were performed before and after the exposure. No impairments of lung functions, blood gases, or blood chemistry were found, but statistical analysis of the data was not reported.

10.6 EXTRAPULMONARY EFFECTS OF OZONE

The high oxidation potential of O_3 has led early investigators to suspect that the major damage from inhalation of this compound resulted from oxidation of labile components in biological systems to produce structural or biochemical lesions (Chapter 10). Initial studies by Buckley et al. (1975) suggested that statistically significant changes ($P < 0.05$) occurred in erythrocytes and sera of seven young adult men following exposure to 980 μg/m^3 (0.50 ppm) of O_3 for 2.75 hr. Erythrocyte membrane fragility, glucose-6-phosphate dehydrogenase, and lactate dehydrogenase enzyme activities increased, while erythrocyte acetylcholinesterase activity and reduced gluthathione levels decreased. Serum gluthathione activity decreased significantly, while serum vitamin E and lipid peroxidation levels increased significantly. These changes were transitory and tended to disappear within several weeks. Although these changes were significant, that the alterations were such as to modify physiological systems or mechanisms is doubtful (see later reports in Table 10-8).

TABLE 10-8. HUMAN EXTRAPULMONARY EFFECTS OF OZONE EXPOSURE

Ozone concentration		Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
μg/m³	ppm					
294 588	0.15 0.30	UV, NBKI	1 hr (mouthpiece) R (11) & CE (29, 43, 66)	No effect on NPSH, G-6-PD, 6-PG-D, GRase, Hb.	6 male	DeLucia and Adams, 1977
392	0.2	ND	0.5-1 hr	Spherocytosis.	e	Brinkman et al., 1964
392 490	0.2 0.25	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	Hb levels decreased. RBC enzymes: LDH increased, G-6-PD increased, AChE decreased. RBC fragility increased. All observed effects were stress related (heat).	20 male 2 female (asthma)	Linn et al., 1978
725	0.37	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals	RBC fragility increased and serum vitamin E increased in Canadians only. RBC enzymes: AChE decreased in both groups.	2 male (Toronto) 2 female (Toronto) 3 male (L.A.) 1 female (L.A.)	Hackney et al., 1977b
784	0.4	CHEM, NBKI	4 hr IE for two 15-min periods	Mild suppression PHA-induced lymphocyte transformation. Questionable decrease in PMN phagocytosis and intracellular killing.	21 male	Peterson et al. (1978a,b)
784	0.4	CHEM, NBKI	4 hr R	No statistically significant depression in T-lymphocyte rosette formation. B-lymphocyte rosette formation with sensitized human erythrocytes was depressed immediately after but not 72 hr and 2 weeks after ozone exposure.	8 male	Savino et al., 1978
784	0.4	CHEM, NBKI	4 hr IE for two 15-min periods	No detectable cytogenetic effect.	26 male	McKenzie et al., 1977
784	0.4	CHEM, NBKI	2.25 hr IE (2xR) @ 15-min intervals	RBC fragility increased. RBC enzymes: AChE decreased; LDH increased in new arrivals. Serum glutathione reductase increased in new arrivals.	6 female (L.A.) 7 female (new arrival) 2 male (new arrival)	Hackney et al., 1976

TABLE 10-8 (continued). HUMAN EXTRAPULMONARY EFFECTS OF OZONE EXPOSURE

Ozone concentration		Measurement^{a,b} method	Exposure duration and activity^{c}	Observed effect(s)^{d}	No. and sex of subjects	Reference
μg/m³	ppm					
784	0.4	CHEM, NBKI	4 days 4 hr/day IE for two 15-min periods	RBC G-6-PD increased. Serum vitamin E increased. Complement C_3 increased.	74 male (divided into four exposure groups)	Chaney et al., 1979
784	0.4	CHEM, NBKI	4 days 4 hr/day	No detectable cytogenetic effects.	30 male	McKenzie, 1982
1176	0.6		2 hr IE for two 15-min periods			
980	0.5	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals ± Vit E	No significant effects.	29 male and female	Hamburger et al., 1979
980	0.5	CHEM, NBKI	2 hr IE (2xR) @ 15-min intervals intervals	No significant effects.	9 male 28 female	Posin et al., 1979
980	0.5	CHEM, NBKI	2.75 hr IE (2xR) @ 15-min intervals	RBC fragility increased. RBC enzymes: LDH increased, G-6-PD increased, AChE decreased, GSH decreased. Serum: GSSRase decreased, vitamin E increased, lipid peroxidation levels increased.	7 male	Buckley et al., 1975
980	0.5	CHEM, NBKI	4 days 2.5 hr/day IE (2xR) @ 15-min intervals	Hb decreased after second exposure. RBC enzymes: GSH decreased after second exposure, 2,3-DPG increased and AChE decreased with successive exposures. Levels tended to stabilize with repeated exposure but did not return to control values.	6 male (Atopic)	Hackney et al., 1978
980	0.5	UV, NBKI	2 hr IE (2xR) @ 15-min intervals	No effect on circulating lymphocytes.	31 male and female	Guerrero et al., 1979

TABLE 10-8 (continued). HUMAN EXTRAPULMONARY EFFECTS OF OZONE EXPOSURE

Ozone concentration		Measurement[a,b] method	Exposure duration and activity[c]	Observed effect(s)[d]	No. and sex of subjects	Reference
μg/m³	ppm					
980	0.5	MAST, NBKI	6-10 hr IE for two 15-min periods	Frequency of chromatid aberrations increased immediately following exposure with a peak in number 2 weeks after exposure (not statistically significant); no change in number of chromosome aberrations.	6 male and female	Merz et al., 1975
1176	0.6	CHEM, NBKI	2 hr IE for two 15-min periods.	Suppression to PHA-induced lymphocyte transformation is questionable.	16 male	Peterson et al., 1981
1960	1.0	ND	10 min	Decreased rate of cutaneous HbO_2 desaturation	e	Brinkman and Lamberts, 1958

[a] Measurement method: MAST = KI-coulometric (Mast meter); CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry; ND = not described.

[b] Calibration method: NBKI = neutral buffered potassium iodide.

[c] Activity level: R = rest; CE = continuous exercise; IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min or in multiples of resting ventilation.

[d] Abbreviations used: NPSH = nonprotein sulfhydryl; G-6-PD = glucose-6-phosphate dehydrogenase; 6-PG-D = 6-phosphogluconate dehydrogenase; GRase = glutathione reductase; Hb = hemoglobin; RBC = red blood cell; LDH = lactate dehydrogenase; AChE = acetylcholinesterase; PHA = phytohemagglutinin; GSSRase = glutathione reductase; GSH = reduced glutathione; 2,3-DPG = 2,3-diphosphoglycerate; HbO_2 = oxyhemoglobin; PMN = polymorphonuclear leukocytes.

[e] Details not given.

In the most comprehensive studies to date concerning the cytogenetic effects of inhaled O_3 in human subjects, McKenzie and co-workers have investigated both chromosome and chromatid aberrations (McKenzie et al., 1977) as well as sister chromatid exchange (SCE) frequencies (McKenzie, 1982). Blood samples from 26 normal male volunteers were collected before O_3 exposure; immediately after exposure; and 3 days, 2 weeks, and 4 weeks after exposure to 784 $\mu g/m^3$ (0.4 ppm) of O_3 for 4 hr. Each subject served as his own control since pre-exposure blood samples were collected. A total of 13,000 human lymphocytes were analyzed cytogenetically. One hundred well-spread, intact metaphase plates were examined per subject per treatment time for chromosome number, breaks, gaps, deletions, fragments, rings, dicentrics, translocations, inversions, triradials, and quadriradials. The data indicated no apparent detectable cytogenetic effect resulting from exposure to O_3 under the conditions of the experiments.

In later studies, McKenzie (1982) investigated the SCE frequency, in addition to the number of chromosomal aberrations in peripheral lymphocytes of human subjects exposed to 784 $\mu g/m^3$ (0.4 ppm) of O_3 for 4 hr on one day and for 4 hr/day on four consecutive days, or to 1176 $\mu g/m^3$ (0.6 ppm) for 2 hr on one day only. One hundred metaphases per blood sample per subject for chromosome aberrations, and 50 metaphases per blood sample per subject were analyzed for SCEs. Each study was conducted on 10 to 30 healthy, nonsmoking human subjects. No statistically significant differences were observed in the frequencies of numerical aberrations, structural aberrations, or SCEs between O_3 pre-exposure and post-exposure values. The nonsignificant differences were observed at all concentrations and durations tested, and in the multiple exposures as well as in the single O_3 exposures.

Chromosome and chromatid aberrations were investigated by Merz et al. (1975) in lymphocytes collected from subjects exposed to 980 $\mu g/m^3$ (0.5 ppm) of O_3 for 6 to 10 hr. Increases in the frequency of chromatid aberrations (achromatic lesions and chromatid deletions) were observed in lymphocytes after O_3 exposure, with a peak in the number of aberrations 2 weeks after exposure. No increase was observed in the number of chromosome aberrations. While these results suggest human genotoxicity after O_3 exposure, the results did not differ significantly from pre-O_3 chromatid aberration frequencies because of the small number (six) of subjects investigated.

Guerrero et al. (1979) exposed 31 male and female subjects to filtered air followed on a second day by 2-hr exposure to 980 $\mu g/m^3$ (0.5 ppm) of O_3. Subjects "lightly" exercised 15 min out of every 30 min. Blood samples were, unfortunately, obtained only at the termination of the exposures. An SCE analysis performed on the circulating lymphocytes showed no change in lymphocyte chromosomes in either condition. However, SCE analysis performed on diploid human fetal lung cells (WI-38) exposed to 0.0, 490, 1470, and 1960 $\mu g/m^3$ (0.0, 0.25, 0.75, and 1.00 ppm) of O_3 for 1 hr in vitro was shown to have a dose-related increase in SCEs. The investigators suggested that the lack of SCE changes in lymphocytes in vivo was attributable to the protective effect of serum and/or another agent.

Peterson and co-workers conducted three studies designed to evaluate the influence of O_3 exposures on leukocyte and lymphocyte function. In 1978, Peterson et al. (1978a) evaluated bactericidal and phagocytic rates in polymorphonuclear leukocytes from blood obtained before each exposure, 4 hr after exposure, as well as 3 and 14 days post-exposure. The 21 subjects were exposed for 4 hr to to 784 $\mu g/m^3$ (0.40 ppm) of O_3 at rest with the exception of two 15-min periods of exercise (700 kgm/min, resulting in a doubling of heart rate). The phagocytic rate and intracellular killing of respirable-size bacteria (Staphylococcus epidermis) was significantly reduced 72 hr after O_3 exposure. No significant effect on the phagocytic rate or intracellular killing was observed immediately after O_3 exposure, or at 2 weeks after O_3 exposure. The nadir of neutrophil function was observed at 72 hours after O_3 exposure. Since the neutrophil has an average lifespan of 6.5 hr, the mechanism by which O_3 produces an effect on the neutrophil at 72 hr is open to speculation. Ozone may produce indirect effects on neutrophils through toxicity to granulocytic stem cells, or by altering humoral factors that facilitate phagocytosis. A similar experimental protocol was used in a subsequent study on 11 subjects with the addition of a clean-air exposure with four subjects (Peterson et al., 1978b). The experimental description is confusing, because variable numbers of subjects were studied under different conditions. In the O_3 764-$\mu g/m^3$ (0.39-ppm) exposure (20 subjects), lymphocyte transformation responses to 2 $\mu g/ml$ and 20 $\mu g/ml$ of phytohemagglutinin (PHA) in cultures indicated significant ($P < 0.01$) suppression to 2 $\mu g/ml$ of PHA in blood obtained immediately post-exposure but no effects with 20 $\mu g/ml$ of PHA. The data, presented only in graphical form, suggested a wide variability in response, and consequently the significance of the observations may be minor. A third study was conducted by these investigators (Peterson et al., 1981) on 16 subjects exposed to 1176 $\mu g/m^3$ (0.6 ppm) of O_3. The protocol of rest, exercise, and blood sampling was similar to that used in their earlier studies except that one additional blood sample was obtained at least 1 to 2 months after the exposure. The relative frequency of lymphocytes in blood and the _in vitro_ blastogenic response of the lymphocytes to PHA, concanavalin A (con A), poleweed mitogen (PWM), and _Candida albicans_ were determined. In the second- and fourth-week blood samples, a significant ($P < 0.05$) reduced response to PHA was observed. No other alterations in function were observed. The significance of these findings remains somewhat tenuous.

Savino et al. (1978) observed that while peripheral blood T-lymphocyte rosette formation was unchanged following exposure of human subjects to 784 $\mu g/m^3$ (0.4 ppm) O_3 for 4 hr, B-lymphocyte rosette formation was significantly depressed. Rosette formation is an _in vitro_ method that measures the binding of antigenic red blood cells with surface membrane sites on lymphocytes. Different antigenic red cells are used to distinguish T from B lymphocytes. A normal B-lymphocyte response was restored by 72 hr after O_3 exposure.

Biochemical parameters (erythrocyte fragility, hematocrit, hemoglobin, erythrocyte glutathione, acetylcholinesterase, glucose-6-phosphate dehydrogenase, and lactic acid dehydrogenase) were determined in blood obtained from subjects given either vitamin E or a placebo (Posin et al., 1979). Exposure conditions were filtered air on day 1 and 980 $\mu g/m^3$ (0.50 ppm) O_3 on day 2; 2 hr of exposure alternating with 15 min of exercise (double the resting minute ventilation) and 15 min of rest. Vitamin E intakes for nine or more weeks were 800 or 1600 IU. The number of subjects and the percent of men and women differed in each of the three studies conducted. No significant differences between the responses of the supplemented and placebo groups to the O_3 exposure were found for any of the parameters measured. Hamburger et al. (1979) obtained blood from the 29 subjects in one of the above three experiments (800 IU vitamin E and placebo). Blood was obtained before and after the 2-hr exposures to filtered air or 980 $\mu g/m^3$ (0.5 ppm) of O_3. No statistically significant change in erythrocyte agglutinability by concanavalin A was found.

In summary, the overall impression of available human data raises doubts that cellular damage or altered function to circulating cells occurs as a consequence of exposure to O_3 concentration under 980 $\mu g/m^3$ (0.5 ppm).

10.7 PEROXYACETYL NITRATE

Subjects exposed to peroxyacetyl nitrate (PAN) complain of eye irritation, blurred vision, eye fatigue, and of the compound's distinctive odor. Smith (1965) had 32 young male subjects breathe orally 0.30 ppm PAN for 5 min at rest and continue to inhale this pollutant during a subsequent 5-min period of light exercise. Oxygen uptake during exercise was found to be statistically higher while breathing PAN than while breathing filtered air. These observations were not confirmed in subsequent studies (Table 10-9). Gliner et al. (1975) studied 10 young men (22 to 26 years of age) and nine older men (44 to 45 years) while they walked at 35 percent max $\dot{V}O_2$ for 3.5 hr of a 4-hr exposure to PAN. The ambient conditions in the chamber were either 25°C or 35°C dry bulb at 30 percent rh and the PAN concentration was either 0.0 or 0.24 ppm. Various measures of cardiorespiratory function were similar in both PAN and filtered-air exposures. A study of 16 older men (40 to 57 years) breathing 0.27 ppm PAN for 40 min found no changes in oxygen uptake during light work (Raven et al., 1974a).

The potential influence of PAN on $\dot{V}O_{2\ max}$ was determined in 20 young men who undertook a 20-min progressive modified Balke test while inhaling 0.27 ppm at ambient conditions of either 25°C (Raven et al. 1974b) or 37°C (Drinkwater et al., 1974). Total exposure time was 40 min. No alterations in cardiorespiratory functions or maximal aerobic capacity due to the pollutants were observed regardless of the ambient temperatures. Raven et al. (1974a) evaluated metabolic, cardiorespiratory, and body temperature responses of seven middle-aged (40 to 57 years) smokers and nine nonsmokers during tests of maximal aerobic power. Ambient conditions were 25°C or 35°C dry bulb and 25 percent rh. These subjects inhaled either filtered air or air containing 0.27 ppm PAN for 40 min. No effects of PAN were found. Effects related to age, smoking history, and ambient temperatures were as anticipated.

In his studies of young men orally inhaling 0.30 ppm PAN, Smith (1965) found a small reduction in MEFR following light exercise but no change in this function during resting exposures. Raven et al. (1976) observed a small but significant (4 percent) reduction in standing FVC in young men after 3.5 hr of light exercise (35 percent $\dot{V}O_{2\ max}$) during a 4-hr exposure to 0.24 ppm PAN.

Drechsler-Parks et al. (1984) studied metabolic and pulmonary function effects in ten nonsmoking young men randomly exposed for 2 hr to each of four conditions: (1) filtered air, (2) 0.30 ppm PAN, (3) 882 $\mu g/m^3$ (0.45 ppm) O_3, and (4) 0.30 ppm PAN + 0.45 ppm O_3 PAN/O_3). The subjects alternated 15-min

TABLE 10-9. ACUTE HUMAN EXPOSURE TO PEROXYACETYL NITRATE

Concentration		Exposure duration and activity[a]	Observed effect(s)[b]	No. and sex of subjects	Reference
μg/m³	ppm				
1187	0.24	4 hr IE (20-30) for 50 min of each hr.	FVC decreased 4% in 10 young subjects after exercise. No significant change in pulmonary function in nine middle-aged subjects. No interaction between exposure, temperature (25° & 35°C), or smoking habit.	19 male	Raven et al., 1976
1187	0.24	4 hr IE (20-30) for 50 min of each hr	No significant changes in submaximal work at 35% $\dot{V}O_{2max}$ in 10 young and nine middle-aged subjects. No interaction between exposure and temperature (25° & 35°C).	19 male	Gliner et al., 1975
1336	0.27	40 min IE (progressive) for 20 min	No significant change in $\dot{V}O_{2max}$ in young nonsmokers (n = 10) or smokers (n = 10) during treadmill walk at 35°.	20 male	Drinkwater et al., 1974
1336	0.27	40 min IE (progressive) for 20 min	No significant change in $\dot{V}O_{2max}$ in middle-aged nonsmokers (n = 9) or smokers (n = 7) during treadmill walk at 25°C and 35°C.	16 male	Raven et al., 1974a
1336	0.27	40 min (mouthpiece) IE (progressive) for 20 min	No significant change in $\dot{V}O_{2max}$ in young nonsmokers (n = 10) or smokers (n = 10) during treadmill walk at 25°C.	20 male	Raven et al., 1974b
1484	0.30	10 min (mouthpiece) IE for 5 min	Oxygen uptake increased with exercise. Maximum expiratory flow rate decreased after exercise.	32 male	Smith, 1965
1484	0.30	2 hr IE(27) with alternating 15-min rest and 20-min exercise	No significant changes in pulmonary function or exercise ventilation with PAN. Simultaneous effect of PAN and 0.45 ppm O_3; decrements in TLC, FVC, $FEV_{1.0}$, and $FEF_{25-75\%}$ were significantly greater (10%) with PAN/O_3 when compared with O_3 alone.	10 male	Drechsler-Parks et al., 1984

[a] Activity level: IE = intermittent exercise; minute ventilation ($\dot{V}_E$) given in L/min.

[b] See Glossary for the definition of symbols.

periods of rest and 20-min periods of moderate exercise ($\dot{V}_E$ = 27 L/min) on a bicycle ergometer during the exposure. Forced expiratory volume and flow were determined before and after exposure and 5 min after each exercise period. Functional residual capacity was determined pre- and postexposure. Heart rate was measured throughout the exposure, and $\dot{V}_E$, $\dot{V}O_2$, f_R, and V_T were measured during the last 2 min of each exercise period. There were no significant changes in exercise $\dot{V}O_2$ or heart rate during any of the pollutant exposures. The changes in breathing patterns occurring during exercise were significant decreases in V_T with exposure to O_3 and PAN/O_3 and significant increases in f_R with PAN/O_3 exposure. No effects on lung function or respiratory symptoms were reported after exposure to filtered air or PAN. Exposure to O_3 and PAN/O_3 produced significant decrements in FVC, FEV_1, FEV_2, FEV_3, $FEF_{25-75\%}$, IC, ERV, and TLC. The decrements in TLC, FVC, FEV_1, and $FEF_{25-75\%}$ were significantly greater (10 percent) with PAN/O_3 exposure and occurred in a shorter period of time when compared with exposure to O_3 alone. A wide range of individual responsiveness to O_3 and PAN/O_3 was noted among subjects; four subjects had greater than 30 percent decrements in FEV_1 while one subject showed no change at all. Symptoms reported after O_3 and PAN/O_3 exposures were similar, although a greater number of symptoms were reported after the PAN/O_3 exposure. The results by Drechsler-Parks et al. (1984) suggest a simultaneous effect of the oxidants PAN and O_3. However, because the large individual responsiveness to O_3 makes direct comparisons to extant data difficult to perform, it is not clear if the greater decrements observed after PAN/O_3 exposure are related to total oxidant load. Additional research is needed to further clarify the relationship between PAN and O_3 at concentrations found in ambient air.

The interaction of PAN and CO was also evaluated in the series of studies on healthy young and middle-aged men exercising on a treadmill (Raven et al., 1974a, 1974b; Drinkwater et al., 1974; Gliner et al., 1975). Both smokers and nonsmokers were exposed to 0.27 ppm PAN and 50 ppm CO. No interactions between CO and PAN were found. Metabolic, body temperature, and cardiorespiratory responses of healthy middle-aged men, nine smokers and seven nonsmokers, were obtained during tests of maximal aerobic power (max $\dot{V}_{O2}$) at ambient temperatures of 25°C and 35°C, rh = 20 percent (Raven et al., 1974a). These subjects were randomly exposed for 40 min in an environmental chamber to each of four conditions, i.e., filtered air, 50 ppm CO, 0.27 ppm PAN, and a combination of 50 ppm of CO and 0.27 ppm of PAN. Carboxyhemoglobin was measured in these subjects. There was no significant change in maximal aerobic power related to the presence of these air pollutants, although total exercising time was lowered in the 25°C environment while exposed to CO. A decrement in max $\dot{V}_{O2}$ was found in middle-aged smokers breathing 50 ppm of CO. Another study conducted under similar pollutant conditions at an ambient temperature of 35°C, 20 percent rh was carried out on 20 young male subjects (10 smokers and 10 nonsmokers) (Drinkwater et al., 1974). Maximal aerobic power was not affected by any pollutant condition. Exposure to CO was effective in reducing work time of the smokers. The same subjects were also involved in a study conducted at 25°C, 20 percent rh under similar pollutant conditions except that they inhaled the pollutants orally for 40 min (Raven et al., 1974b). Exposure to the two pollutants singly or in combination produced only minor, nonsignificant alterations in cardiorespiratory and temperature regulatory parameters. The influence of PAN and CO, singly or in combination, was evaluated in 10 young (22 to 26 years) and nine middle-aged (45 to 55 years) men performing submaximal work (35 percent max $\dot{V}_{O2}$) for 210 min (Gliner et al., 1975). Five subjects in each age group were smokers. Studies were conducted at two different ambient temperatures, i.e., 25°C and 35°C, rh 30 percent. The pollutant concentrations were 0.25 ppm of PAN and 50 ppm of CO. Two physiological alterations were reported. Stroke volume decreased during long-term work, being enhanced in the higher ambient temperatures. Heart rate was significantly ($P < 0.05$) higher when exercise was being performed during the CO exposures. No other alterations were found in relation to the pollutants. There were no differences in response related to age.

10.8 SUMMARY

A number of important controlled studies discussed in this chapter have reported significant decrements in pulmonary function associated with O_3 exposure (Table 10-10). In most of the studies reported, greatest attention has been accorded decrements in $FEV_{1.0}$, as this variable represents a summation of changes in both volume and resistance. While this is true, it must be pointed out that for exposure concentrations critical to the standard-setting process (i.e., ≤ 0.3 ppm O_3), the observed decrements in $FEV_{1.0}$ primarily reflect FVC decrements of similar magnitude, with little or no contribution from changes in resistance.

TABLE 10-10 SUMMARY TABLE: CONTROLLED HUMAN EXPOSURE TO OZONE

Ozone[a] concentration µg/m^3	ppm	Measurement[b,c] method	Exposure duration	Activity[d] level (V_E)	Observed effects(s)	No. and sex of subjects	Reference
HEALTHY ADULT SUBJECTS AT REST							
627 1960	0.32 1.0	MAST, NBKI	2 hr	R	Specific airway resistance increased with acetylcholine challenge; subjective symptoms in 3/14 at 0.32 ppm and 8/14 at 1.0 ppm.	13 male 1 female	König et al., 1980
980	0.5	CHEM, NBKI	2 hr	R (10)	Decrement in forced expiratory volume and flow.	40 male (divided into four exposure groups)	Folinsbee et al., 1978
980 1470	0.50 0.75	CHEM, NBKI	2 hr	R (8)	Decrement in forced expiratory volume and flow.	8 male 7 female	Horvath et al., 1979
EXERCISING HEALTHY ADULTS							
235 353 470 588 784	0.12 0.18 0.24 0.30 0.40	CHEM, UV	2.5 hr	IE (65) @ 15-min intervals	Decrement in forced expiratory volume and flow suggested at 0.12 ppm with larger decrements at ≥ 0.18 ppm; respiratory frequency and specific airway resistance increased and tidal volume decreased at ≥ 0.24 ppm; coughing reported at all concentrations, pain and shortness of breath at ≥ 0.24 ppm.	135 male (divided into six exposure groups)	McDonnell et al., 1983
314 470 627	0.16 0.24 0.32	UV, UV	1 hr	CE (57)	Small decrements in forced expiratory volume at 0.16 ppm with larger decrements at ≥0.24 ppm; lower-respiratory symptoms increased at ≥0.16 ppm.	42 male 8 female (competitive bicyclists)	Avol et al., 1984
353 470 588 784	0.18 0.24 0.30 0.40	CHEM, UV	2.5 hr	IE (65) @15-min intervals	Individual responses to O_3 were highly reproducible for periods as long as 10 months; large intersubject variability in response due to intrinsic responsiveness to O_3.	32 male	McDonnell et al., 1985a
392 686	0.20 0.35	UV, UV	1 hr (mouth-piece)	IE (77.5) @ variable competitive intervals CE (77.5)	Decrement in forced expiratory volume and flow with IE and CE; subjective symptoms increased with O_3 concentration and may limit performance; respiratory frequency increased and tidal volume decreased with CE.	10 male (distance runners)	Adams and Schelegle, 1983

TABLE 10-10 (continued). SUMMARY TABLE: CONTROLLED HUMAN EXPOSURE TO OZONE

Ozone[a] concentration μg/m³	ppm	Measurement[b,c] method	Exposure duration	Activity[d] level (V_E)	Observed effects(s)	No. and sex of subjects	Reference
392 823 980	0.2 0.42 0.50	UV, UV	2 hr	IE (30 for male, 18 for female subjects) @ 15-min intervals	Repeated daily exposure to 0.2 ppm did not affect response at higher exposure concentrations (0.42 or 0.50 ppm); large intersubject variability but individual pulmonary function responses were highly reproducible.	8 male 13 female	Gliner et al., 1983
392 490	0.20 0.25	UV, UV	2 hr	IE (68) (4) 14-min periods	Large intersubject variability in response; significant concentration-response relationships for pulmonary function and respiratory symptoms.	20 male	Kulle et al., 1985
412	0.21	UV, UV	1 hr	CE (81)	Decrement in forced expiratory volume and flow; subjective symptoms may limit performance.	6 male 1 female (distance cyclists)	Folinsbee et al., 1984
490	0.25	UV, UV	1 hr	CE (63)	Increased responsiveness to O_3 lasts for 24 hr, may persist in some subjects for 48 hr, but is generally lost within 72 hr.	19 male 7 female	Folinsbee and Horvath, 1986
588 980	0.3 0.5	CHEM, NBKI	2 hr	R (10), IE (31, 50, 67) @ 15-min intervals	Decrement in forced expiratory volume and flow; the magnitude of the change was related to O_3 concentration and V_E. Total lung capacity and inspiratory capacity decreased with IE (50, 67); no change in airway resistance or residual volume even at highest IE (67). No significant changes in pulmonary function were observed at 0.1 ppm.	40 male (divided into four exposure groups)	Folinsbee et al., 1978
725 980 1470	0.37 0.50 0.75	MAST, NBKI	2 hr	R (11) & IE (29) @ 15-min intervals	Good correlation between dose (concentration x $\dot{V}_E$) and decrement in forced expiratory volume and flow.	20 male 8 female (divided into six exposure groups)	Silverman et al., 1976
784	0.4	UV, NBKI	2 hr	IE (2xR) @ 15-min intervals	Specific airway resistance increased with histamine challenge; no changes were observed at concentrations of 0.2 ppm.	12 male 7 female (divided into three exposure groups)	Dimeo et al., 1981
784	0.4	CHEM, NBKI & MAST, NBKI	3 hr	IE (4-5xR)	Decrement in forced expiratory volume and SG_{aw} was greatest on the 2nd of 5 exposure days; attenuated response by the 4th day of exposure.	10 male 4 female	Farrell et al., 1979

TABLE 10-10 (continued). SUMMARY TABLE: CONTROLLED HUMAN EXPOSURE TO OZONE

Ozone[a] concentration μg/m³	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration	Activity[d] level (V_E)	Observed effects(s)	No. and sex of subjects	Reference
784	0.4	CHEM, UV	3 hr	IE (4-5xR) for 15 min	Decrement in forced expiratory volume was greatest on the 2nd of 5 exposure days; attenuation of response occurred by the 5th day and persisted for 4 to 7 days. Enhanced bronchoreactivity with methacholine on the first 3 days; attenuation of response occurred by the 4th and 5th day and persisted for > 7 days.	13 male 11 female (divided into two exposure groups)	Kulle et al., 1982b
784	0.4	CHEM, UV	2.5 hr	IE (71) @ 15-min intervals	Atropine pretreatment prevented the increased R_{aw} observed with O_3 exposure, partially blocked the decreased forced expiratory flow, but did not prevent the O_3-induced decreases in FVC and TLC, changes in exercise ventilation, or respiratory symptoms.	8 male	Beckett et al., 1985
823	0.42	UV, UV	2 hr	IE (30)	Decrement in forced expiratory volume and flow greatest on the 2nd of 5 exposure days; attenuation of response occurred by the 5th day and persisted for < 14 days with considerable intersubject variability.	24 male	Horvath et al., 1981
882	0.45	UV, UV	2 hr	IE (27) @ 20-min intervals	Increased responsiveness to O_3 was found with a 2nd O_3 challenge given 48 hr after the initial exposure.	1 male 5 female	Bedi et al., 1985
921	0.47	UV, NBKI	2 hr	IE (3xR)	Decrement in forced expiratory volume and flow greatest on the 2nd of 4 exposure days; attenuation of response occurred by the 4th day and persisted for 4 days.	8 male 3 female	Linn et al., 1982b
980	0.5	MAST, NBKI	6 hr	IE (44) for two 15-min periods	Small decrements in forced expiratory volume and specific airway conductance.	19 male 1 female	Kerr et al., 1975
1176	0.6	UV, NBKI	2 hr (noseclip)	IE (2xR) @ 15-min intervals	Specific airway resistance increased in 7 nonatopic subjects with histamine and methacholine and in 9 atopic subjects with histamine.	11 male 5 female (divided by history of atopy)	Holtzman et al., 1979
1470	0.75	MAST, NBKI	2 hr	IE (2xR) @ 15-min intervals	Decrements in spirometric variables (20%-55%); residual volume and closing capacity increased.	12 male	Hazucha et al., 1973

TABLE 10-10. (continued) SUMMARY TABLE: CONTROLLED HUMAN EXPOSURE TO OZONE

Ozone[a] concentration µg/m³	ppm	Measurement[b,c] method	Exposure duration	Activity[d] level (V_E)	Observed effects(s)	No. and sex of subjects	Reference
EXERCISING HEALTHY CHILDREN							
235	0.12	CHEM, UV	2.5 hr	IE (39) @15-min intervals	Small decrements in forced expiratory volume, persisting for 24 hr. No subjective symptoms.	23 male (8-11 yrs)	McDonnell et al., 1985b,c
ADULT ASTHMATICS							
392	0.2	CHEM, NBKI	2 hr	IE (2xR) @ 15-min intervals	No significant changes in pulmonary function. Small changes in blood biochemistry. Increase in symptom frequency reported.	20 male 2 female	Linn et al., 1978
490	0.25	CHEM, NBKI	2 hr	R	No significant changes in pulmonary function.	5 males 12 female	Silverman, 1979
ADOLESCENT ASTHMATICS							
235	0.12	UV	1 hr (mouthpiece)	R	No significant changes in pulmonary function or symptoms.	4 male 6 female (11-18 yrs)	Koenig et al., 1985
SUBJECTS WITH CHRONIC OBSTRUCTIVE LUNG DISEASE							
235	0.12	UV, NBKI	1 hr	IE (variable) @ 15-min intervals	No significant changes in forced expiratory performance or symptoms. Decreased arterial oxygen saturation during exercise was observed.	18 male 7 female	Linn et al., 1982a
353 490	0.18 0.25	UV, NBKI	1 hr	IE (variable) @ 15-min intervals	No significant changes in forced expiratory performance or symptoms. Group mean arterial oxygen saturation was not altered by O_3 exposure.	15 male 13 female	Linn et al., 1983
392 588	0.2 0.3	CHEM, NBKI	2 hr	IE (28) for 7.5 min each half hour	No significant changes in pulmonary function or symptoms. Decreased arterial oxygen saturation during exposure to 0.2 ppm.	13 male	Solic et al., 1982 Kehrl et al., 1983, 1985
784	0.41	UV, UV	3 hr	IE (4-5xR) for 15 min	Small decreases in FVC and $FEV_{3.0}$.	17 male 3 female	Kulle et al., 1984

[a] Ranked by lowest observed effect level.

[b] Measurement method: MAST = KI-Coulometric (Mast meter); CHEM = gas phase chemiluminescence; UV = ultraviolet photometry.

[c] Calibration method: NBKI = neutral buffered potassium iodide; UV = ultraviolet photometry.

[d] Minute ventilation reported in L/min or as a multiple of resting ventilation. R = rest; IE = intermittent exercise; CE = continuous exercise.

Results from studies of at-rest exposures to O_3 have demonstrated decrements in forced expiratory volumes and flows occurring at and above 980 $\mu g/m^3$ (0.5 ppm) of O_3 (Folinsbee et al., 1978; Horvath et al., 1979). Airway resistance is not clearly affected at these O_3 concentrations. At or below 588 $\mu g/m^3$ (0.3 ppm) of O_3, changes in pulmonary function do not occur during at rest exposure (Folinsbee et al., 1978), but the occurrence of some O_3-induced pulmonary symptoms has been suggested (König et al., 1980).

With moderate intermittent exercise at a $\dot{V}_E$ of 30 to 50 L/min, decrements in forced expiratory volumes and flows have been observed at and above 588 $\mu g/m^3$ (0.30 ppm) of O_3 (Folinsbee et al., 1978). With heavy intermittent exercise ($\dot{V}_E$ = 65 L/min), pulmonary symptoms are present and decrements in forced expiratory volumes and flows are suggested to occur following 2-hr exposures to 235 $\mu g/m^3$ (0.12 ppm) of O_3 (McDonnell et al., 1983). Symptoms are present and decrements in forced expiratory volumes and flows definitely occur at 314 to 470 $\mu g/m^3$ (0.16 to 0.24 ppm) of O_3 following 1 hr of continuous heavy exercise at a $\dot{V}_E$ of 57 L/min (Avol et al., 1984) or very heavy exercise at a $\dot{V}_E$ of 80 to 90 L/min (Adams and Schelegle, 1983; Folinsbee et al., 1984) and following 2 hr of intermittent heavy exercise at a $\dot{V}_E$ of 65 to 68 L/min (McDonnell et al., 1983; Kulle et al., 1985). Airway resistance is only modestly affected with moderate exercise (Kerr et al., 1975; Farrell et al., 1979) or even with heavy exercise while exposed at levels as high as 980 $\mu g/m^3$ (0.50 ppm) O_3 (Folinsbee et al., 1978; McDonnell et al., 1983). Increased f_R and decreased V_T, while maintaining the same $\dot{V}_E$, occur with prolonged heavy exercise when exposed at 392 to 470 $\mu g/m^3$ (0.20 to 0.24 ppm) of O_3 (McDonnell et al., 1983; Adams and Schelegle, 1983). While an increase in RV has been reported to result from exposure to 1470 $\mu g/m^3$ (0.75 ppm) of O_3 (Hazucha et al., 1973), changes in RV have not been observed following exposures to 980 $\mu g/m^3$ (0.50 ppm) of O_3 or less, even with heavy exercise (Folinsbee et al., 1978). Decreases in TLC and IC have been observed to result from exposures to 980 $\mu g/m^3$ (0.50 ppm) of O_3 or less, with moderate and heavy exercise (Folinsbee et al., 1978).

Recovery of the lung from the effects of O_3 exposure consists of return of pulmonary function (FVC, FEV_1, and SR_{aw}) to preexposure levels. The time course of this recovery is related to the magnitude of the O_3-induced functional decrement (i.e., recovery from small decrements is rapid). Despite apparent functional recovery of most subjects within 24 hr, an enhanced responsiveness to a second O_3 challenge may persist in some subjects for up to 48 hr (Bedi et al., 1985; Folinsbee and Horvath, 1986).

Group mean decrements in pulmonary function can be predicted with some degree of accuracy when expressed as a function of effective dose of O_3, the simple product of O_3 concentration, $\dot{V}_E$, and exposure duration (Silverman et al., 1976). The relative contribution of these variables to pulmonary decrements is greater for O_3 concentration than for $\dot{V}_E$. A greater degree of predictive accuracy is obtained if the contribution of these variables is appropriately weighted (Folinsbee et al., 1978). However, several additional factors make the interpretation of prediction equations more difficult. There is considerable intersubject variability in the magnitude of individual pulmonary function responses to O_3 (Horvath et al., 1981; Gliner et al, 1983; McDonnell et al., 1983; Kulle et al., 1985). Individual responses to a given O_3 concentration have been shown to be quite reproducible (Gliner et al., 1983; McDonnell et al., 1985a), indicating that some individuals are consistently more responsive to O_3 than are others. No information is available to account for these differences. Considering the great variability in individual pulmonary responses to O_3 exposure, prediction equations that only use some form of effective dose are not adequate for predicting individual responses to O_3.

In addition to overt changes in pulmonary function, enhanced nonspecific bronchial reactivity has been observed following exposures to O_3 concentrations ≥ 588 $\mu g/m^3$ (0.3 ppm) (Holtzman et al., 1979; König et al., 1980; Dimeo et al., 1981). Exposure to 392 $\mu g/m^3$ (0.2 ppm) of O_3 with intermittent light exercise does not affect nonspecific bronchial reactivity (Dimeo et al., 1981).

Changes in forced expiratory volumes and flows resulting from O_3 exposure reflect reduced maximal inspiratory position (inspiratory capacity) (Folinsbee et al., 1978). These changes, as well as altered ventilatory control and the occurrence of respiratory symptoms, most likely result from sensitization or stimulation of airway irritant receptors (Folinsbee et al., 1978; Holtzman et al., 1979; McDonnell et al., 1983). The increased airways resistance observed following O_3 exposure is probably initiated by a similar mechanism. Different efferent pathways have been proposed (Beckett et al., 1985) to account for the lack of correlation between individual changes in SR_{aw} and FVC (McDonnell et al., 1983). The increased responsiveness of airways to histamine and methacholine following O_3 exposure most likely results from an O_3-induced increase in airways permeability or from an alteration of smooth muscle characteristics.

Decrements in pulmonary function were not observed for adult asthmatics exposed for 2 hours at rest (Silverman, 1979) or with intermittent light exercise (Linn et al., 1978) to O_3 concentrations of 490 $\mu g/m^3$ (0.25 ppm) and less. Likewise, no significant changes in pulmonary function or symptoms were found in adolescent asthmatics exposed for 1 hr at rest to 235 $\mu g/m^3$ (0.12 ppm) of O_3 (Koenig et al., 1985). Although these results indicate that asthmatics are not more responsive to O_3 than are healthy subjects, experimental-design considerations in reported studies suggest that this issue is still unresolved. For patients with COLD performing light to moderate intermittent exercise, no decrements in pulmonary function are observed for 1- and 2-hr exposures to O_3 concentrations of 588 $\mu g/m^3$ (0.30 ppm) and less (Linn et al., 1982a, 1983; Solic et al., 1982; Kehrl et al., 1983, 1985) and only small decreases in forced expiratory volume are observed for 3-hr exposures of chronic bronchitics to 804 $\mu g/m^3$ (0.41 ppm) (Kulle et al., 1984). Small decreases in SaO_2 have also been observed in some of these studies but not in others; therefore, interpretation of these decreases and their clinical significance is uncertain.

Many variables have not been adequately addressed in the available clinical data. Information derived from O_3 exposure of smokers and nonsmokers is sparse and somewhat inconsistent, perhaps partly because of undocumented variability in smoking histories. Although some degree of attenuation appears to occur in smokers, all current results should be interpreted with caution. Further and more precise studies are required to answer the complex problems associated with personal and ambient pollutant exposures. Possible age differences in response to O_3 have not been explored systematically. Young adults usually provide the subject population, and where subjects of differing age are combined, the groups studied are often too small in number to make adequate statistical comparisons. Children (boys, aged 8 to 11 yr) have been the subjects in only one study (McDonnell et al., 1985b) and nonstatistical comparison with adult males exposed under identical conditions has indicated that the effects of O_3 on lung spirometry were very similar (McDonnell et al., 1985c). While a few studies have investigated sex differences, they have not conclusively demonstrated that men and women respond differently to O_3, and consideration of differences in pulmonary capacities have not been adequately taken into account. Environmental conditions such as heat and relative humidity may enhance subjective symptoms and physiological impairment following O_3 exposure, but the results so far indicate that the effects are no more than additive.

In addition, there may be considerable interaction between these variables that may result in modification of interpretations made based on available information.

During repeated daily exposures to O_3, decrements in pulmonary function are greatest on the second exposure day (Farrell et al., 1979; Horvath et al., 1981; Kulle et al., 1982b; Linn et al., 1982b); thereafter, pulmonary responsiveness to O_3 is attenuated with smaller decrements on each successive day than on the day before until the fourth or fifth exposure day when small decrements or no changes are observed. Following a sequence [illegible] eated daily exposures, this attenuated pulmonary responsiveness persist[illegible] 3 (Kulle et al., 1982b; Linn et al., 1982b) to 7 (Horvath et al., 198[illegible]. Repeated daily exposures to a given low effective dose of O_3 does not [illegible] the magnitude of decrements in pulmonary function resulting from exp[illegible] at a higher effective dose of O_3 (Gliner et al., 1983).

There is some evidence suggesting that exercise perform[illegible] ay be limited by exposure to O_3. Decrements in forced expiratory flow o[illegible] ing with O_3 exposure during prolonged heavy exercise ($\dot{V}_E$ = 65 to 81 L/min) along with increased f_R and decreased V_T might be expected to produce ventilatory limitations at near maximal exercise. Results from exposure to ozone during high exercise levels (68 to 75 percent of max $\dot{V}O_2$) indicate that discomfort associated with maximal ventilation may be an important factor in limiting performance (Adams and Schelegle, 1983; Folinsbee et al., 1984). However, there is not enough data available to adequately address this issue.

No consistent cytogenetic or functional changes have been demonstrated in circulating cells from human subjects exposed to O_3 concentrations as high as 784 to 1176 $\mu g/m^3$ (0.4 to 0.6 ppm). Chromosome or chromatid aberrations would therefore be unlikely at lower O_3 levels. Limited data have indicated that O_3 can interfere with biochemical mechanisms in blood erythrocytes and sera but the physiological significance of these studies is questionable.

No significant enhancement of respiratory effects has been consistently demonstrated for combined exposures of O_3 with SO_2, NO_2, and sulfuric acid or particulate aerosols or with multiple combinations of these pollutants. Most of the available studies with other photochemical oxidants have been limited to studies on the effects of peroxyacetyl nitrate (PAN) on healthy young and middle-aged males during intermittent moderate exercise. No significant effects were observed at PAN concentrations of 0.25 to 0.30 ppm, which are higher than the daily maximum concentrations of PAN reported for relatively high oxidant areas (0.047 ppm). One study (Drechsler-Parks et al., 1984) suggested a possible simultaneous effect of PAN and O_3; however, there are not enough data to evaluate the significance of this effect. Further studies are also required to evaluate the relationships between O_3 and the more complex mix of pollutants found in the natural environment.

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11. FIELD AND EPIDEMIOLOGICAL STUDIES OF THE EFFECTS OF OZONE AND OTHER PHOTOCHEMICAL OXIDANTS

11.1 INTRODUCTION

This chapter critically assesses field and epidemiological studies of health effects linked to ambient air exposure to ozone and other photochemical oxidants. In order to characterize the nature and extent of such effects, the chapter (1) delineates types of health effects associated with exposures to ozone or photochemical oxidants in ambient air; (2) assesses the degree to which relationships between exposures to these agents and observed effects are quantitative; and (3) identifies population groups at greatest risk for such health effects. Studies of both acute and chronic exposure effects are summarized and discussed. Tables are provided to give the reader an overview of the studies reviewed in this chapter.

In many of the epidemiological studies available in the literature, exposure data or health endpoint measurements were used that were inadequate or unreliable for quantifying exposure-effect relationships. Also, results from these studies have often been confounded by factors such as variations in activity levels and time spent out of doors, cigarette smoking, coexisting pollutants, weather, and socioeconomic status. Thus, selection of those studies thought to be most useful in deriving health criteria for ozone or oxidants is of critical importance. Assessment of the relative scientific quality of epidemiological studies for standard-setting purposes is a difficult and often controversial problem; therefore, the following general guidelines (as modified from U.S. Environmental Protection Agency, 1982) have been suggested as useful for appraising individual studies:

1. The aerometric data are adequate for characterizing geographic or temporal differences in pollutant exposures of study populations in the range(s) of pollutant concentrations evaluated.
2. The study populations are well defined and allow for statistically adequate comparisons between groups or temporal analyses within groups.
3. The health endpoints are scientifically plausible for the pollutant being studied, and the methods for measuring those endpoints are adequately characterized and implemented.
4. The statistical analyses are appropriate and properly performed, and the data analyzed have been subjected to adequate quality control.

5. Potentially confounding or covarying factors are adequately controlled for or taken into account.

6. The reported findings are internally consistent and biologically plausible.

For present purposes, studies most fully satisfying these suggested criteria provide the most useful information on exposure-effect or exposure-response relationships associated with ambient air levels of ozone or photochemical oxidants likely to occur in the United States during the next 5 years. Accordingly, the following additional guidelines were used to select studies for detailed discussion: (1) the results provide information on quantitative relationships between health effects and ambient air ozone or oxidant concentrations with emphasis on concentrations less than or equal to 0.5 ppm (measurement methods and calibrations are reported when available); and (2) the report has been peer-reviewed and is in the open literature or is in press. A number of recent studies not meeting the above guidelines but considered to be sources of additional supportive information are also discussed below and their limitations noted.

The remaining studies not rigorously meeting all of these guidelines are tabulated chronologically by year of publication within each subject area. Since the lack of quantitative exposure data is a frequently noted limitation of epidemiological studies, an attempt has been made to provide as detailed a description as possible of the photochemical oxidant concentrations and averaging times reported in the original manuscripts. In addition, the tables summarize comments on earlier studies described in detail in the 1978 EPA criteria document for ozone and other photochemical oxidants (U.S. Environmental Protection Agency, 1978).

11.2 FIELD STUDIES OF EFFECTS OF ACUTE EXPOSURE TO OZONE AND OTHER PHOTOCHEMICAL OXIDANTS

For the purposes of this document, field studies are defined as laboratory experiments where the postulated cause of an effect in the population or environment is tested by removing it under controlled conditions (Morris, 1975; Mausner and Bahn, 1974; American Thoracic Society, 1978; World Health Organization, 1983). Field studies of symptoms and pulmonary function contain elements of both controlled human exposure studies (Chapter 10) and of epidemiologic studies. These studies employ observations made in the field along with the methods and better experimental control typical of controlled exposure studies. Studies classified here as field studies used exposure chambers but exposed subjects to ambient air containing the pollutants of interest rather than to artificially generated pollutants, as well as to clean air as a control. These studies thus form a bridge or continuum between the studies discussed in the preceding chapter (Chapter 10) and the epidemiological studies assessed later in this chapter.

11.2.1 Symptoms and Pulmonary Function in Field Studies of Ambient Air Exposures

Researchers at the Ranchos Los Amigos Hospital in California (Linn et al., 1980, 1982, 1983; Avol et al., 1983, 1984, 1985a,b) have used a mobile laboratory containing an exposure chamber to study the effects of ambient air exposures on symptoms and pulmonary function in high-oxidant (Duarte) and low-oxidant (Hawthorne) areas of the Los Angeles Basin. In these field studies, pre- and post-exercise measurements of pulmonary function, often used in controlled human exposure studies, were made to compare the effects of short-term exposures to ozone and oxidants in ambient air versus clean air (sham control) exposures. The subject characteristics and experimental conditions in the respective studies are summarized in Table 11-1. The mobile laboratory has been described previously (Avol et al., 1979), as have the methods for studies of lung function.

In 1978 Linn et al. (1980, 1983) evaluated 30 asthmatic and 34 normal subjects exposed to ambient and purified air in a mobile laboratory in Duarte, CA, during two periods separated by 3 weeks. Only five subjects were smokers, and the two groups were similar with respect to the age, height, and sex of subjects. Asthmatic subjects had heterogeneous disease characteristics, as determined by questionnaire responses. Of the "normal" group, 25 subjects were considered allergic based on a history of upper respiratory allergy or reported undiagnosed wheeze that they called "allergic." No definitive clinical evaluations were performed to verify the allergic status of these subjects. Ozone, nitrogen oxides (NO_x), sulfur dioxide (SO_2), sulfates, and total suspended particulate matter (TSP) were monitored inside and outside the chamber at 5-min intervals. Measurements of O_3 by the ultraviolet (UV) method were calibrated against California Air Resources Board (CARB) reference standards and were corrected to those obtained by the KI method.

Ozone and particulate pollutants predominated in the ambient air mixture, as shown in Table 11-1 for the 1978 study (Linn et al., 1980, 1983). Ozone

TABLE 11-1. SUBJECT CHARACTERISTICS AND EXPERIMENTAL CONDITIONS IN THE MOBILE LABORATORY STUDIES

Subjects/conditions	Year and place of study					
	1978, Duarte[a]	1979, Hawthorne[b]	1980, Duarte[c]	1981, Duarte[d]	1982, Duarte[e]	1983, Duarte[f]
Subject characteristics:						
Total number	64	64	60	98	50	59
Males	26	26	45	57	42	46
Asthmatics	30	21	7	50	0	2
Smokers	5	14	8	7	3	0
Avg. age, yr ± SD	30 ± 10	34 ± 11	30 ± 11	28 ± 8	26 ± 7	14 ± 1
Avg. ht, cm ± SD	170 ± 10	170 ± 12	173 ± 15	172 ± 9	177 ± 8	162 ± 13
Avg. wt, kg ± SD	70 ± 14	69 ± 16	69 ± 10	67 ± 11	70 ± 10	54 ± 13
Experimental conditions:						
Exercise level	light intermittent	light intermittent	heavy continuous	heavy continuous	heavy continuous	moderate continuous
Exposure duration	2 hr (p.m.)	2 hr (a.m.)	1 hr (p.m.)	1 hr (p.m.)	1 hr (p.m.)	1 hr (p.m.)
Pollutant concentration, mean ± SD						
O_3, ppm[g]	0.174 ± 0.068	0.022 ± 0.011	0.165 ± 0.059	0.156 ± 0.055	0.153 ± 0.025	0.144 ± 0.043
SO_2, ppm	0.012 ± 0.003	0.018 ± 0.099	0.009 ± 0.005	0.005 ± 0.033	0.006 ± 0.004	0.006 ± 0.001
NO_2, ppm	0.069 ± 0.014	0.056 ± 0.033	0.050 ± 0.028	0.062 ± 0.023	0.040 ± 0.016	0.055 ± 0.011
CO, ppm	2.9 ± 1.1	1.6 ± 0.9	3.1 ± 2.0	2.2 ± 0.7	2.2 ± 0.8	1.1 ± 0.3
Particulate:						
Total, μg/m^3	182 ± 42	112 ± 45	227 ± 76	166 ± 52	295 ± 52	152 ± 29
$SO_4^=$, μg/m^3	16 ± 7	13 ± 6	17 ± 12	9 ± 4	13 ± 8	5 ± 4
NO_3, μg/m^3	h	19 ± 10	22 ± 9	32 ± 10	40 ± 10	19 ± 4

[a] Linn et al. (1980, 1983).

[b] Linn et al. (1982, 1983).

[c] Linn et al. (1983); Avol et al. (1983).

[d] Linn et al. (1983); Avol et al. (1983).

[e] Avol et al. (1984, 1985c).

[f] Avol et al. (1985a,b).

[g] Ultraviolet photometer calibration method.

[h] Measurements unsatisfactory due to artifact nitrate formation on filters.

Source: Adapted from Linn et al. (1983).

levels (corrected to the KI method) averaged 427 $\mu g/m^3$ (0.22 ppm) inside the mobile laboratory chamber and 509 $\mu g/m^3$ (0.26 ppm) outside the laboratory during ambient air exposures; and 7.8 $\mu g/m^3$ (0.004 ppm) during purified air exposures. The respective maximum O_3 concentrations were 498 ± 186 $\mu g/m^3$ (0.25 ± 0.10 ppm) inside; 597 ± 217 $\mu g/m^3$ (0.31 ± 0.11 ppm) outside; and 19 ± 17 $\mu g/m^3$ (0.01 ± 0.009 ppm) in purified air. Levels of TSP averaged 182 $\mu g/m^3$ inside the chamber and 244 $\mu g/m^3$ outside the laboratory during ambient air exposures, but 49 $\mu g/m^3$ inside the chamber during purified-air exposures. Average NO_2, SO_2, CO, and sulfate levels inside the chamber were uniformly low during ambient-air exposures (as shown in Table 11-1) and were even lower during purified-air exposures (i.e., 0.015 ppm for NO_2; 0.009 ppm for SO_2; 2.8 ppm for CO; 0.9 ppm for sulfates). Gases were monitored continuously, with inside and outside air sampled alternately for 5-min periods. Particles were measured during testing inside and outside the laboratory. Temperature and humidity were controlled inside the laboratory.

During the exposure studies (Tuesday through Friday), four subjects (maximum) were tested sequentially in the morning at 15-min intervals, each first breathing purified air at rest followed by "pre-exposure" lung-function tests. Ambient-air chamber tests were performed in the early afternoon (after odors were masked by a brief outside exposure). The ambient-air exposure period lasted 2 hr and included exercise on bicycle ergometers for the first 15 min of each half-hour; this was followed by "post-exposure" lung function testing during continuing ambient-air exposure. Ergometer workloads ranged from 150 to 300 kg-m/min and were sufficient to double the respiratory minute ventilation relative to resting level. Lung function measures before and after exposure were compared by t-tests and nonparametric methods. The purified-air control study for each subject took place at least 3 weeks after the ambient-air exposure session, with identical procedures except for purified air in place of the ambient. Note that 12 healthy subjects from the project staff were tested apart from the study cohort in order to validate various aspects of the study. The validation tests were performed to determine whether there were any gross differences in response to indoor and outdoor ambient exposures. While no significant differences were found in this comparison, small differences would have been difficult to detect because of the small number of subjects tested.

In the main set of experiments (Linn et al., 1980, 1983), the asthmatic group experienced greater changes from baseline in residual volume (RV) and peak flow measurements with exercise than did the "normals," based on data adjusted for subject age, height, and weight. The magnitude of these changes did not correlate with age. Both groups showed similar changes in most of the other lung-function measurements. Regression analysis showed no significant associations of functional changes with TSP, total sulfate, total NH_3, or NO_2. Increasing O_3 was correlated with decreasing peak flow and 1-sec forced expiratory volume (FEV_1). No explanation was given for the observed association of increasing CO with increasing RV and with the slope of the alveolar plateau (SBNT). Increasing SO_2 was significantly associated with increasing RV and total lung capacity (TLC). In multiple regression analysis, O_3 was the variable contributing the most variation in FEV_1 and maximum expiratory flow ($\dot{V}_{max25\%}$), as well as in the FEV_1 normalized for forced vital capacity ($FEV_1/FVC\%$), TLC, and pulmonary resistance (R_t) in the normal/allergic group. Although other pollutant variables contributed to the observed effects, none did so consistently. Apart from O_3, functional changes on control days (intraindividual variability), smoking habits, and age appeared to explain the functional changes in normals/ allergics during exposure. In asthmatics, all pollutant variables except TSP were significant in one or more analyses, but not all consistently. Asthmatics and normals/allergics also had significantly increased symptom scores during ambient air exposure sessions (Figure 11-1).

Nine of 12 subjects from this study (Linn et al., 1980, 1983) known to be highly reactive to O_3 (four from the normal/allergic group and five asthmatics, a similar proportion from each group), who had experienced a fall in FEV_1 greater than 200 ml during ambient exposure (compared to purified-air exposure), underwent a controlled 2-hr exposure experiment at 392 $\mu g/m^3$ (0.2 ppm) with intermittent exercise. Among these nine reactive subjects, the mean FEV_1 change in the ambient exposure was -273 ± 196 ml (-7.8 ± 6.3 percent of pre-exposure). This change was significantly greater than the mean change of -72 ± 173 ml (3.1 ± 6.6 percent pre-exposure) in the control setting. Although the authors suggested the possibility that ambient photochemical pollution may be more toxic than chamber exposures to purified air containing only ozone, other explanations for the differences were given, including the effect of regression toward the mean. More direct comparative findings published recently by Avol et al. (1984) (see following text) showed no differences in response between chamber exposures to oxidant-polluted ambient air and purified air containing a controlled concentration of O_3. Normal/allergic subjects in the validation

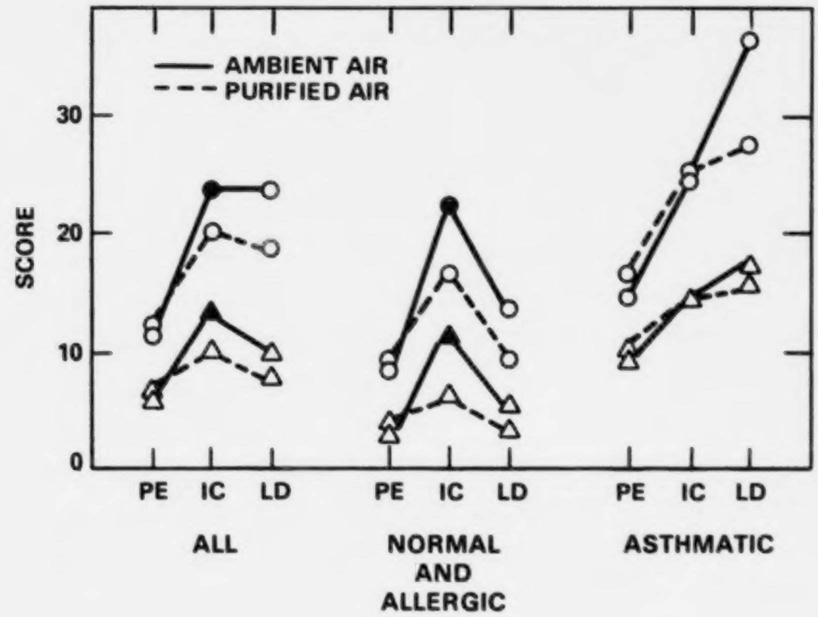

Figure 11-1. Changes in mean symptom score with exposure for all subjects, for normal and allergic subjects, and for asthmatic subjects. PE = pre-exposure; IC = in chamber (near end of exposure period); LD = later in day. Circles (○ or ●) indicate total symptom scores; triangles (△ or ▲) indicate lower-respiratory symptom scores. Solid symbols indicate that ambient exposure score is significantly higher for indicated time period and/or increased significantly more relative to pre-exposure value. Open symbols indicate that the difference between ambient and purified air scores was not significant.

Source: Adapted from Linn et al. (1980).

studies also showed similar findings in the exposure chambers compared to the outside ambient air when the levels were similar inside and out.

Linn et al. (1982, 1983) repeated the initial experiment (Linn et al., 1980) with 64 different subjects, ages 18 to 55, in Hawthorne, CA, which had low O_3 levels (0.04 ± 0.02 ppm, 82 ± 39 $\mu g/m^3$) but elevated levels of other pollutants. They found no statistically significant lung-function or symptom changes, and they concluded that O_3 was primarily responsible for the effects seen in the original study.

In 1980, a third experiment (Linn et al., 1983; Avol et al., 1983) was conducted at the original oxidant-polluted location (Duarte) with 60 physically fit subjects, aged 18 to 55, who exercised heavily (four to five times resting minute ventilation) and continuously for 1 hr. The mean O_3 concentration was 314 $\mu g/m^3$ (0.16 ppm) in ambient air (measured by the UV method). Total reported symptoms did not differ significantly between exposure and control (purified-air) conditions. For the complete group, small functional decrements in FEV_1 were found (3.3 percent loss, $P < 0.01$), more or less comparable to those in the original (1978) study. A number of the subjects showed functional losses during exposure that were still present after a 1-hr recovery period at rest in filtered air. Those in the most reactive quartile (those who experienced 320 to 1120-ml losses, versus control) were compared with the least reactive quartile (increases of 60 to 350 ml). They did not differ by age, height, sex, smoking, medication use, prevalence of atopy, or asthma. Negative FEV_1 changes occurred more frequently (34 of 47 cases) at O_3 exposure concentrations above 235 $\mu g/m^3$ (0.12 ppm), up to the maximum observed (549 $\mu g/m^3$; 0.28 ppm) in the total study group ($P = 0.02$). Even at the upper end of this range, however, a number of subjects showed no decrement in function. The authors stated that the marked functional losses measured in the most reactive subjects in this study were not necessarily accompanied by symptoms, nor were they related to obvious prior physical or clinical status.

In 1981, a fourth study (Linn et al., 1983; Avol et al., 1983) presented data on 98 subjects, including 50 asthmatics, who were exposed in Duarte to mean O_3 levels of 306 $\mu g/m^3$ (0.156 ppm) and 166 $\mu g/m^3$ TSP (lower than in 1980). The highest O_3 exposure concentration was 431 $\mu g/m^3$ (0.22 ppm), which was lower than the levels measured in 1980. The subjects were exposed to heavy, continuous exercise (though at slightly lower exercise ventilation levels than in 1980). The normal subjects showed a pattern of forced expiratory changes that were similar to those reported in 1980; however, the mean

FEV_1 decrease with exposure to ambient air was much smaller. The only significant change reported for this group was for FVC ($P < 0.003$). The asthmatics had decrements in forced expiratory performance during both exposures, but the mean FEV_1 decrease remained depressed for up to 3 hr after exposure to ambient air. Maximum mean changes in FVC and FEV_1 for asthmatics after exposure to ambient air were 122 ml and 89 ml, respectively, with the former returning more quickly to control levels. The value for $\dot{V}_{max50\%}$ was more variable with a maximum mean change of 132 L/s after exposure to ambient air. There were also significant interactions of ambient and purified air after exposure in asthmatics for FEV_1 and $\dot{V}_{max50\%}$.

The subject population was expanded in the summer of 1982 to include well-conditioned athletes undergoing 1 hr of continuous heavy exercise (six to ten times resting minute ventilation) (Avol et al., 1984, 1985c) Volunteer competitive bicyclists (n=50) were exposed in the mobile chamber to purified air containing 0, 157, 314, 470, and 627 $\mu g/m^3$ (0, 0.08, 0.16, 0.24, and 0.32 ppm) O_3 and to ambient air in the Duarte location. Pollution conditions were milder than in previous summers so that comparable ambient exposure data were available for only 48 subjects (Table 11-1). Mean concentrations during ambient exposures were 294 $\mu g/m^3$ (0.15 ppm) O_3 with a range of 235 to 372 $\mu g/m^3$ (0.12 to 0.19 ppm) and 295 $\mu g/m^3$ total suspended particulate matter (TSP). Mean particulate nitrate and sulfate concentrations were 40 $\mu g/m^3$ and 13 $\mu g/m^3$, respectively. For the controlled exposure studies, no functional decrements in FEV_1 were found at 0 or 157 $\mu g/m^3$ (0 or 0.08 ppm) O_3; however, statistically significant decrements were found at 314, 470, and 627 $\mu g/m^3$ (0.16, 0.24, and 0.32 ppm) O_3 (see Section 10.2.3). Symptom increases generally paralleled the FEV_1 decrements (Figure 11-2). Statistically significant decrements in FEV_1 were also observed during the ambient exposure studies (5 percent) and were not significantly different from those obtained with 0.16 ppm O_3. At the generated O_3 concentrations of 0.24 and 0.32 ppm, an increasing number of subjects could not complete the 1 hr of exercise without reducing their workloads. Exposure to ambient air or 0.16 ppm O_3 produced no decreases in workloads, even though statistically significant decrements in lung function and increased symptoms did occur. Comparisons on an individual basis showed that ambient exposure responses differed only randomly from predictions based on the generated O_3 concentration-response information. Symptom increases during ambient exposure were slightly less than predicted. Thus, no evidence

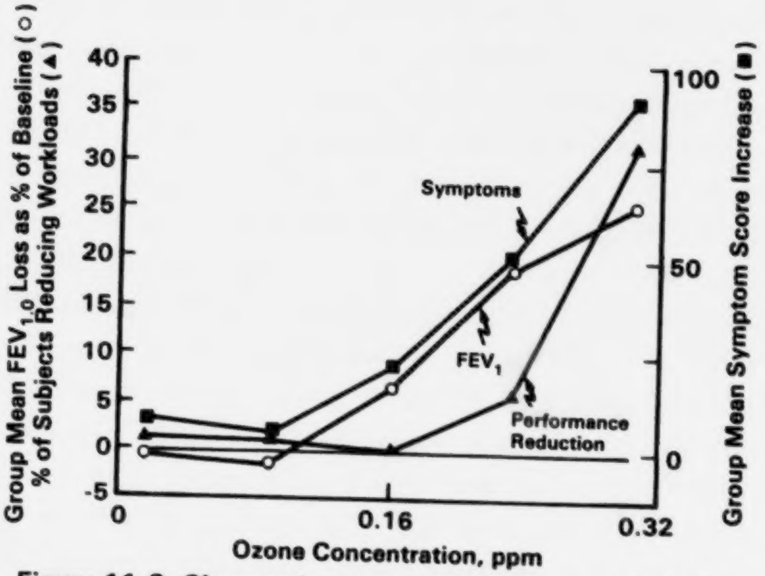

Figure 11-2. Changes in group mean responses, including $FEV_{1.0}$, symptoms, and exercise performance in 50 competitive cyclists exercising continuously for 1 hr while exposed to ozone.

Source: Adapted from Avol et al. (1985c).

was found to suggest that any pollutant other than O_3 contributed to the observed effects produced by ambient air.

The mobile laboratory was used again in Duarte, CA, during the summer of 1983 to determine if younger subjects were affected by exposure to ambient levels of photochemical oxidants. Avol et al. (1985a,b) studied forced expiratory function and symptom responses in 59 healthy adolescents, 12 to 15 years of age (Table 11-1). Each subject received a screening examination including medical history, pulmonary function tests, resting EKG, and exercise stress test. All subjects denied smoking regularly. Fifteen of the subjects had a history of allergy and two of the subjects gave a history of childhood asthma but denied recent asthmatic symptoms. The subjects were randomly exposed to purified air and to ambient air containing 282 $\mu g/m^3$ (0.144 ppm) O_3 and 153 $\mu g/m^3$ total suspended particulates while continuously exercising on bicycle ergometers at moderate levels ($\dot{V}_E$ = 32 L/min) for 1 hr. Pulmonary function tests were performed pre- and post-exposure. Symptoms were recorded at 15-min intervals and immediately post-exercise. Following the exposure period, the subjects rested in purified air for 1 hr, after which symptoms and pulmonary function were measured again. After ambient exposure, there were statistically significant decrements in FVC (2.1 percent), $FEV_{0.75}$ (4.0 percent), $FEV_{1.0}$ (3.7 percent), and PEFR (4.4 percent) relative to control exposure. Although some reversal of these changes was evident at 1 hr post-exposure, decrements in pulmonary function were still present compared to the preexposure levels. A linear regression analysis showed that individual $FEV_{1.0}$ responses were negatively correlated ($r = 0.37$, $P < 0.01$) with individual ambient O_3 exposure concentrations. Analysis of the data set revealed no significant differences in responses between the fifteen "allergic" subjects and the rest of the group. In addition, although girls tended to show larger decreases in $FEV_{1.0}$ with ambient exposure than boys (7.5 percent and 3.4 percent, respectively), the difference was not statistically significant. The authors attributed the lack of significance as possibly due to the smallnumber ($n = 13$) of girls in the study. There were no significant increases in symptoms with ambient exposure relative to control. The lack of symptoms in adolescents at ambient O_3 concentrations that produce statistically significant decrements in pulmonary function is an interesting and potentially important observation from this study, since adults exposed in the mobile laboratory under similar conditions report symptoms of lower respiratory irritation accompanying decrements in forced expiratory function (Linn et al., 1980, 1983; Avol et al., 1983, 1984).

Factors contributing to the differences in response between adolescents and adults are not yet known.

11.2.2 Symptoms and Pulmonary Function in Field or Simulated High-Altitude Studies

Early reports of high O_3 concentrations in aircraft flying at high altitudes prompted a series of field and high-altitude simulation studies. In 1973, Bischof reported that O_3 concentrations (measured by a Comhyr ECC meter) during 14 spring polar flights (1967-1971) varied from 0.1 to 0.7 ppm, with 1-hr peaks above 1.0 ppm occurring, despite ventilation. More recently, Daubs (1980) reported O_3 concentrations in Boeing 747 aircraft ranging from 0.04 to 0.65 ppm, with short-term (2 to 3 min) levels as high as 1.035 ppm. Other reports (U.S. House of Representatives, 1980; Broad, 1979) have indicated that O_3 concentrations in high-altitude aircraft can reach excessively high levels; for example, on a flight from New York to Tokyo a time-weighted concentration of 0.438 ppm was recorded, with a maximum of 1.689 ppm and a 2-hr exposure of 0.328 ppm.*

Flight attendants and passengers in high-altitude aircraft have complained of certain symptoms (chest pain, substernal pain, cough), which are identical to those typically reported in subjects exposed to O_3 and other photochemical oxidants (see 11.3.1.1). The symptoms were most prevalent during late winter and early spring flights. Similar symptoms have also been observed in more systematic studies of high-altitude effects, such as (1) the study by Reed et al. (1980), in which symptoms among 1,330 flight attendants were found to be related to aircraft aircraft type and altitude duration but not to sex, medical history, residence, or years of work; and (2) the Tashkin et al. (1983) study, in which increased O_3-related symptoms were reported by flight attendants on Boeing 747SP (higher-altitude) flights in comparison to attendants on lower-flying 747 flights. In neither of these two studies, however, were concentrations of O_3 or other photochemical oxidants measured in the aircraft.

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*Note that, as ambient pressure decreases at high altitude, O_3 concentrations remain the same as expressed in terms of ppm levels, but O_3 mass concentrations (in $\mu g/m^3$) decrease in direct proportion to increasing altitudes. Therefore, knowledge of prevailing atmosphere pressure and temperature is generally needed for correct conversion of ppm O_3 readings to $\mu g/m^3$ O_3 concentrations under specific measurement conditions.

In a series of altitude-simulation studies, Lategola and associates (1980a,b) attempted a more quantitative evaluation of effects on cardiopulmonary function and symptoms associated with O_3 exposures of male and female flight attendants, crew, and passengers. Two studies (Lategola et al., 1980a) were conducted on young surrogates of a mildly exercising flight attendant population, while a third study (Lategola et al., 1980b) evaluated older surrogates for sedentary airline passengers and cockpit crew. All studies simulated in-flight environmental conditions at 1829 m (6000 ft) and all subjects served as their own controls. The results indicate increased symptoms and pulmonary function decrements among nonsmoking normal adult subjects at 0.30 ppm, but not 0.2 ppm under light exercise conditions. It should be noted that the O_3 levels used in the Lategola studies are generally lower than O_3 concentrations reported to occur in certain aircraft at high altitudes, as are the simulated altitudes employed in the studies.

11.3 EPIDEMIOLOGICAL STUDIES OF EFFECTS OF ACUTE EXPOSURE

Effects of the acute exposure of communities to photochemical oxidants are generally assessed by comparing the functional or clinical status of residents during periods of high and low O_3 or oxidant concentrations. Occasionally, two or more communities with different concentrations are compared. The concentrations measured have been 24-hr averages, maximum hourly averages, or instantaneous peaks.

11.3.1. Acute Exposure Morbidity Effects

For purposes of this document, indices of acute morbidity associated with photochemical oxidants include the incidence of acute respiratory illnesses; symptom aggravation in healthy subjects and in patients with asthma and other chronic lung diseases; and effects on pulmonary function, athletic performance, auto accident rates, school absenteeism, and hospital admissions.

11.3.1.1 Symptom Aggravation in Healthy Populations. Various symptoms, including eye irritation, headache, and respiratory irritation, have been reported during ambient air exposure in a number of studies (Table 11-2). Eye irritation, however, has not been associated with O_3 exposure in controlled laboratory studies (Chapter 10). This symptom has been associated with other photochemical oxidants such as peroxyacetyl nitrate (PAN) and with formaldehyde, acrolein, and other organic photochemical reaction products (National Air Pollution Control Administration, 1970; Altshuller, 1977; U.S. Environmental

Protection Agency, 1978; National Research Council, 1977; Okawada et al., 1979). Of the biological effects caused by or aggravated by photochemical air pollution, eye irritation appears to have one of the lowest thresholds. It also appears to be a short-term, reversible effect, however, since damage to conjunctiva and subjacent tissue has not been reported.

Qualitatively, the occurrence of an association between photochemical oxidant exposure and symptoms such as cough, chest discomfort, and headache is plausible, given similar findings of occupational exposure to oxidants (see 11.3.1.7) and of controlled human exposure studies (Chapter 10). The primary issues in question, however, in the studies cited in Table 11-2, are: (1) the composition of the mixture to which the subjects were exposed; (2) the concentrations and averaging times for oxidants in ambient air; and (3) the adequacy of methodologic controls for other pollutants, meteorological variables, and non-environmental factors in the analysis. For these reasons, the studies are of limited use for developing quantitative exposure-response relationships for ambient oxidant exposures.

11.3.1.2 Altered Performance. The possible effects of photochemical oxidant pollution on athletic and driving performance have been examined in studies described in Table 11-3. The absence of definitive monitoring data for important pollutants as well as confounding by environmental conditions such as temperature and relative humidity detracts from the quantitative usefulness of these studies. Qualitatively, however, the epidemiological findings relative to athletic performance are consistent with the evidence from field studies (Section 11.2.1) and from controlled human exposure studies (Section 10.4) indicating that exercise performance may be limited by exposure to O_3.

11.3.1.3 Acute Effects on Pulmonary Function. A summary of studies on the acute pulmonary function effects of photochemical oxidant pollution is given in Table 11-4. Previously reviewed studies (U.S. Environmental Protection Agency, 1978) suggested a possible association between decrements in pulmonary function in children and ambient ozone concentrations in Tucson, Arizona (Lebowitz et al., 1974) and Tokyo, Japan (Kagawa and Toyama, 1975; Kagawa et al., 1976). An additional study (McMillan et al., 1969) comparing acute effects in children residing in high- and low-oxidant areas of Los Angeles failed to show any significant differences in pulmonary function. None of these studies, however, meets the criteria necessary for developing quantitative exposure-response relationships for ambient ozone exposures.

TABLE 11-2. SYMPTOM AGGRAVATION IN HEALTHY POPULATIONS EXPOSED TO PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.08-0.50 max 1-hr/day (1954) 0.04-0.78 max 1-hr/day (1955) 0.05-0.49 max 1-hr/day (1956)	Oxidant	Panel studies of office and factory workers in Los Angeles during 1954-1956.	Eye irritation increased with oxidant concentration; no discrete oxidant threshold. Although oxidants explained a higher proportion of the variation in eye irritation, other pollutants were associated with this symptom.	Renzetti and Gobran, 1957[a]
≤0.27 (@ 11:00 a.m. daily)	Oxidant	Effectiveness of air filtration for removing eye irritants in 40 female telephone company employees over 123 work days in Los Angeles from May to November 1956.	Increased eye irritation associated with oxidant concentration and temperature in the nonfiltered room; severity increased above 0.10 ppm. No correlations with NO_2 or PM; however, other pollutants were not measured.	Richardson and Middleton, 1957[a], 1958[a]
<0.04-0.50 max 1-hr/day	Oxidant	Symptom rates from daily diaries of students at two nursing schools in Los Angeles from October 1961 to June 1964. Maximum hourly oxidant concentrations from two monitors located within 0.9 to 2 miles of both hospitals.	Eye discomfort reported at oxidant levels between 0.15 and 0.19 ppm, cough at 0.30 to 0.39 ppm, headache and chest discomfort at 0.25 to 0.29 ppm. Symptom frequencies related more closely to oxidants than CO, NO_2, or temperature, although rigorous statistical treatment is lacking.	Hammer et al., 1974[a]
≤0.3 max 1-hr(?)/day	Oxidant	Daily symptom rates from 854 students in Tokyo during July 1972 to June 1973. Measurement methods for oxidant, NO, NO_2, SO_2, and PM were not reported.	Highest correlations reported between symptoms and oxidants; increased rates for eye irritation, cough, headache, and sore throat on days with max. hourly oxidant >0.10 ppm; no significant correlations with SO_2, NO_2 or NO, although some symptoms were correlated with temperature. Effects of acute respiratory illness were not considered; measurement methods not reported.	Makino and Mizoguchi, 1975[a]
0.07-0.19 max 1-hr/day	Oxidant	Questionnaire survey on subjective symptom rates at two junior high schools in Osaka, Japan during the fall of 1972.	Symptoms classified as (a) eye irritation, (b) cough and sore throat, and (c) nausea, dizziness, and numbness of the extremities; symptom rate and distribution correlated with physical exercise. Findings point out variable symptom distribution from multiple pollutants in ambient air.	Shimizu, 1975[a]

TABLE 11-2 (continued). SYMPTOM AGGRAVATION IN HEALTHY POPULATIONS EXPOSED TO PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
$\leq$0.39 max (undefined)	Oxidant	Survey of student health during 180 days in 1975.	Number of students reporting symptoms increased with increasing oxidant concentration. No symptom rates reported; questionnaire use presented likely bias; other pollutants were not considered.	Japanese Environmental Agency, 1976[a]
$\leq$0.23 max 1-hr/day	Oxidant	Questionnaire survey on subjective symptoms in 515 students at a junior high school in Tokyo from May to July 1974; maximum hourly oxidant concentrations by KI.	Differences between high- and low-oxidant days in symptom rates for eye irritation and lacrimation, sore throat, and dyspnea. Other pollutants, particularly SO_2, SO_x, or acrolein, may have been contributing factors.	Shimizu et al., 1976[a]
			Increased symptom rates for eye irritation, sore throat, headache, and cough on days with oxidant >0.15 ppm compared to days with oxidant <0.10 ppm. Some symptoms were correlated with SO_2, PM, and rh; however, not all possible environmental variables were considered.	Mizoguchi et al., 1977[a]
0.02-0.21 daily maxima (undefined)	Oxidant	Association between eye irritation and photochemical oxidants in 71 Tokyo high school students for 7 days during two summer sessions; daily maximum oxidant concentrations by KI; tear lysozyme, pH, and eye exam measured daily.	Tear lysozyme and pH decreased on two highest oxidant days compared to two lowest oxidant days; eye irritation incidence rates increased with oxidant concentrations >0.1 ppm; eye irritation produced by HCHO, PAN, and PBZN.	Okawada et al., 1979

[a] Reviewed in U.S. Environmental Protection Agency (1978).

TABLE 11-3. ALTERED PERFORMANCE ASSOCIATED WITH EXPOSURE TO PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.03-0.30 max 1-hr/day	Oxidant	Athletic performance of student cross-country track runners in 21 competitive meets at a high school in Los Angeles County from 1959 to 1968. Daily maximum hourly concentrations of oxidants, NO, NO_2, CO, and PM by LA-APCD.	Percentage of team members failing to improve their performance increased with increasing oxidant concentration in the hour before the race; however, convincing individual linear relationships were not demonstrated.	Wayne et al., 1967[a]
0.06-0.38 max 1-hr/day		Data extended to include the seasons of 1966 to 1968.	Inverse relationship between running speed and speed and oxidant after correcting for average speed, time, season, and temperature. No correlation with NO_x, CO, or PM; however, SO_2 was not examined.	Herman, 1972[a]
0.02-0.24 max 1-hr/day	Oxidant	Association of automobile accidents with days of elevated hourly oxidant concentrations in Los Angeles from August through October for 1963 and 1965.	Accident rates were higher on days with hourly oxidant levels >0.15 ppm compared to days <0.10 ppm. Other pollutants were not evaluated. Sample size reduced by excluding accidents involving alcohol, drugs, mechanical failure, rain, or fog.	Ury, 1968[a]
		Association of automobile accidents in Los Angeles with elevated oxidant concentrations from the summers of 1963 and 1965 and with CO concentrations from the winters of 1964-1965 and 1965-1966.	Strong relationship between accident rates and oxidant levels; temporal pattern suggests the importance of oxidant precursors; no consistent relationship with lagged oxidant concentration or with CO concentrations. Other pollutants, possibly NO_x and SO_x, may have confounded the association; questionable effect of traffic density.	Ury et al., 1972[a]

[a] Reviewed in U.S. Environmental Protection Agency (1978).

TABLE 11-4. ACUTE EFFECTS OF PHOTOCHEMICAL OXIDANT POLLUTION ON PULMONARY FUNCTION OF CHILDREN AND ADULTS

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.01-0.67 daily maxima (undefined)	Oxidant	Comparison of ventilatory performance in two groups of third-grade children residing in high (n=50) and low (n=28) oxidant areas of Los Angeles from November 1966 to October 1967.	No correlation between acute effects on PEFR (Wright Peak Flow Meter) and oxidant concentrations; however, persistently higher PEFR and greater variance were obtained from the children residing in the high oxidant area; possible confounding by respiratory infections.	McMillan et al., 1969[a]
0.01-0.12 range of hourly averages for 1 day	Oxidant	Combined effects of air pollution and weather on the ventilatory function of exercising children, adolescents, and adults in Tucson, Arizona during the spring and summer of 1972.	Significant post-exercise decreases in lung function were observed in adolescents but not adults; however, differences in exercise regimens suggest a possible exercise effect. Monitors recording hourly peak oxidant concentrations for adolescents and adults were at least 3 miles away; no oxidant data given for children's study. TSP may have contributed to the observed effect.	Lebowitz et al., 1974[a]
0.01-0.15 max 1-hr/day 0.03-0.17 max 1-hr/day	Ozone Oxidant	Effects of environmental factors on the pulmonary function of 21 children, aged 11 yrs, at an elementary school in Tokyo, Japan from June to December 1972; hourly average concentrations of oxidant (NBKI), O_3 (CHEM), NO_2, NO, HC, and PM measured on top of the three-story school.	Pulmonary function correlated with temperature far more than any other environmental variable; O_3, NO, SO_2, and HC were the pollutants most frequently correlated with changes in pulmonary function; O_3 was correlated with Raw, SGaw, and FVC in only 25% of the subjects. Partial analyses after correcting for temperature reduced the number of significant correlations.	Kagawa and Toyama, 1975[a]
<0.30 averaged over each 2-hr study period	Ozone	Effects of high- and low-temperature seasons on the pulmonary function of 19 children at an elementary school in Tokyo, Japan from November 1972 to October 1973; hourly average concentrations of O_3, NO, NO_2, SO_2, and PM were measured at the school.	Temperature was positively correlated with Raw, $\dot{V}_{50}$, and $\dot{V}_{25}$, and negatively correlated with SGaw; however, the effect of temperature on Raw was season-dependent. O_3 was positively correlated with Raw and negatively correlated with SGaw in both high- and low-temperature seasons; however, correlations were more consistent in the low-temperature period when O_3 was lowest (<0.10 ppm); partial analyses after correcting for temperature still revealed significant O_3 correlations with Raw. Five subjects showed correlations of function and multiple environmental factors, indicating selective sensitivity in the population.	Kagawa et al., 1976[a]

TABLE 11-4 (continued). ACUTE EFFECTS OF PHOTOCHEMICAL OXIDANT POLLUTION ON PULMONARY FUNCTION OF CHILDREN AND ADULTS

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.046-0.122 max 1-hr/day	Ozone	Effects of ambient photochemical oxidant exposure on pulmonary function of 83 children (aged 8 to 13) at a 2-week day camp in Indiana, PA during the summer of 1980; 1-hr peak O_3 concentrations were estimated by regional exposure modeling techniques; 6-hr ambient TSP and H_2SO_4 were monitored at the campsite.	Significant relationship for peak flow (Wright Peak Flow Meter) and daily peak O_3 for 23 children; FVC and FEV_1 were significantly lower on 1 day when the O_3 peak was 0.11 ppm compared to days when the O_3 peak was <0.08 ppm. Analysis of regression slopes does not demonstrate any conclusive associations for sex, other pollutants, or ambient temperature. Questionable exposure modelling raises uncertainty about the quantitative interpretation of these results.	Lippmann et al., 1983b
0.09-0.12 max 1-hr/day	Ozone	As part of a community population sample of 117 families from Tucson, AZ, ventilatory function was studied in 24 healthy children and young adults (aged 8 to 25 yrs) for an 11-month period in 1979 and 1980; 1-hr maximum concentrations of O_3 (CHEM), NO_2, CO, and daily levels of TSP, allergens, and weather variables were monitored at central stations within ½ mile of each cluster of subjects.	Correlation of peak flow (Wright Peak Flow Meter) with average maximum hourly O_3 was not significant; after correcting for season and other pollutants, O_3 and TSP were negatively correlated with peak flow; use of multifactor analysis to control for person days, weather variables, CO, NO_2, and TSP showed significant independent correlations of O_3 with peak flow and significant interactions between O_3 and TSP and O_3 and temperature. Regressions of residual and predicted $\dot{V}$max with O_3 were also significant. Small number of subjects and interaction with other environmental conditions limit the quantitative interpretations of these studies.	Lebowitz et al., 1983b, 1985b; Lebowitz, 1984b
0.02-0.14 max 1-hr/day	Ozone	Effects of ambient photochemical oxidant exposure on pulmonary function of healthy active children (aged 7 to 12) at a summer day camp in Mendham, NJ from July 12 to August 12, 1982; state regional pollution monitoring of O_3 (CHEM), TSP (H^+, $SO_4^=$, and NO_3), temperature, and rh at a station 6 km from the camp.	Linear regression and correlation coefficient analyses between O_3 and pulmonary function (FVC, FEV, PEFR, and MMEF) showed a significant association for PEFR only. Girls appeared to be more susceptible than boys but there was no statistical treatment of the differences. Large variability in regression slopes suggests effects from other environmental conditions (temp, $SO_4^=$, H^+); results of aerosol sampling were not reported and other pollutants were not considered. Lack of significant effect for FEV_1 and FVC which have lower coefficients of variation than PEFR is questionable. In addition, difficulty in judging the relationship between O_3 and acid sulfates or other environmental conditions limits the quantitative use of these studies.	Lippmann and Lioy, 1985b; Bock et al., 1985b; Lioy et al., 1985b.

TABLE 11-4 (continued). ACUTE EFFECTS OF PHOTOCHEMICAL OXIDANT POLLUTION ON PULMONARY FUNCTION OF CHILDREN AND ADULTS

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.004-0.135 avg time-weighted 15-min max	Ozone	Pulmonary function of healthy adults exercising vigorously at a high school track near Houston, TX during May-October, 1981. Continuous monitoring of O_3 (CHEM), SO_2, NO_2, CO, temperature, and rh at the track averaged over 15-min intervals during the time of running; 12-hr averages for fine inhalable particulates.	Simple linear regression analysis showed a significant association between decreased lung function and increasing O_3 concentration; however, after adjusting for rh, the changes were no longer statistically significant. Weighted multiple linear regression analysis adjusted for temperature and rh was not significant for O_3. Other pollutants were not considered.	Selwyn et al., 1985[b]

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[a] Reviewed in U.S. Environmental Protection Agency (1978).

[b] See text for discussion.

Lippmann et al. (1983) studied 83 nonsmoking, middle-class, healthy children (ages 8 to 13) during a 2-week summer day camp program in Indiana, PA. The children exercised outdoors most of the time. Afternoon measurements included baseline and post-exercise spirometry (water-filled, no noseclips). Peak flow rates were obtained by Mini-Wright® Peak Flow Meter at the beginning of the day or at lunch, adjusted for both age and height. No day-of-week effect was seen. Ambient air levels of TSP, hydrogen ions, and sulfates were monitored by a high-volume sampler on the rooftop of the day camp building. Ozone concentrations were estimated as a weighted average of data extrapolated from a monitoring site 20 mi south and a site 60 mi west, using two models that yielded O_3 estimates within ±16 $\mu g/m^3$ (0.008 ppm) on the average. Estimated 1-hr peak O_3 levels (early afternoon) varied from 90 to 249 $\mu g/m^3$ (0.046 to 0.122 ppm), and TSP levels were ≤ 103 $\mu g/m^3$ (6-hr samples) and maximum sulfuric acid (H_2SO_4) concentrations were ≤ 6.3 $\mu g/m^3$.

Lippmann et al. (1983) reported significant inverse correlations between FVC and FEV_1 and estimated maximum 1-hr O_3 levels for 4 or more days on which O_3 concentrations covered a twofold range. Differences in correlations (i.e., slopes) were not related to other pollutants (TSP, H_2SO_4) or ambient temperatures. Qualitatively, the Lippmann et al. (1983) study results suggest low-level O_3 effects; however, because exposure modeling (rather than on-site monitoring) was used to estimate O_3 levels, and because the effects were seen almost entirely on one day of the study, there is uncertainty about the precise quantitative interpretation of these findings.

A similar group of children was studied during the summer at a day camp in Mendham, NJ (Lippmann and Lioy, 1985; Bock et al., 1985; Lioy et al., 1985). Pulmonary function data were obtained from the children, aged 7 to 13 years, during 16 days of a 5-week period from July 12 to August 12, 1982. In order to provide better air monitoring data, O_3 concentrations were measured (UV) at the Mendham camp site and at a NJ sampling station 3.5 mi away. Only data from the sampling station were used in the analysis. The average highest peak 1-hr O_3 concentration measured on a study day was 280 $\mu g/m^3$ (0.143 ppm); values ranged from 39 to 353 $\mu g/m^3$ (0.02 to 0.19 ppm) O_3 during the 5-week period. Daily averages for ambient temperature, relative humidity, and precipitation were provided by the National Weather Service. Ambient aerosol samples were also analyzed on a daily basis, but the results were not reported. A linear regression was calculated for each child between peak 1-hr O_3 and each of four measures: FVC, FEV_1, PEFR, and MMEF. In addition, a summary weighted correlation coefficient was calculated for all subjects. No adjustments were made for covariates. Linear regressions were negative except for FVC in boys. Decrements in PEFR were significantly correlated with peak O_3 exposure but there were no significant correlations with FVC, FEV_1, or MMEF.

Several comparisons can be made between the data reported by Lippmann et al. (1983) and those reported by Lippmann and Lioy (1985), Bock et al. (1985), and Lioy et al. (1985). There were 39 children (22 girls, 17 boys) in the follow-up study for whom sufficient data existed for linear regression analysis. The children in Mendham, NJ, were not as physically active as the children studied in the previous study in Indiana, PA, which may account for some observed differences in results from the two studies. While O_3-dependent changes in PEFR were reported in both studies, the authors did not observe the O_3-dependent change in FVC and FEV_1 in the follow-up study that they found in the previous study. This lack of a significant effect for FVC and FEV_1, which are known to have smaller coefficients of variation than PEFR, is surprising, especially considering the higher O_3 concentrations reported in Mendham, NJ. Concentrations of inhalable particulate matter were also reported to be higher in association with a large-scale regional photochemical smog episode which may have had some effect on baseline lung function (Lioy et al., 1985). In addition, adjustments for covariates such as temperature and relative humidity, which might influence lung function, would have strengthened the reported results. The differences in transient reponses to O_3, the lack of definitive exposure data for other pollutants (particularly ambient aerosols), and the lack of adjustment for covariates limit the usefulness of these studies for determining quantitative exposure-response relationships for O_3.

Lebowitz et al. (1983, 1985) and Lebowitz (1984) measured daily lung function in 24 Tucson, AZ, residents, aged 5 to 25 years. The subjects were part of a stratified sample of families from geographic clusters of a large community population under study. Over an 11-month period in 1979 and 1980, randomly chosen subsets of these subjects were tested during each season of the year. Measurements of peak flow were made in the late afternoon, using a Mini-Wright® Peak Flow Meter (Wright, 1978; Williams, 1979; van As, 1982; Lebowitz et al., 1982b). All age- and height-adjusted baseline peak flows were within the published normal range. To adjust for seasonal effects and for inter-individual differences in means and variances, the daily peak flow for each person was transformed into a standard normal variable. Seasonal means and standard deviations were then used to generate daily z-scores, or standardized deviations from seasonal averages.

Regional ambient O_3 (measured by UV), CO, and NO_2 were monitored daily at three sites in the Tucson basin (Lebowitz et al., 1984). Every 6 days, 24-hr TSP was measured at 12 sites, including stations at the center of each cluster of subjects within a 0.25- to 0.5-mi radius. Since previous ambient monitoring showed significant homogeneity of O_3 in the basin, average regional values were used for analysis of all geographic clusters, and closest-station values for individual clusters. Comparisons showed no significant changes in results when using regional averages or closest daily hourly maximum values. Indoor and outdoor monitoring was conducted in a random cluster sample of 41 representative houses. Measurements of air pollutants, pollen, bacilli, fungi, algae, temperature, and humidity were recorded once in each home for 72 hr during the two-year study period. Regional daily ambient maximum hourly O_3 went up to 239 $\mu g/m^3$ (0.12 ppm) and was highest in the summer months. Indoor O_3 concentrations were between 0 and 69 $\mu g/m^3$ (0 and 0.035 ppm). Levels of CO were less than 2.4 ppm (2736 g/m^3) indoors and 3.8 to 4.9 ppm (4332 to 5586 g/m^3) outdoors. Indoor CO was correlated with gas-stove use only. Daily average ambient NO_2 ranged from 0.001 to 0.331 ppm (2 to 662 $\mu g/m^3$). Outdoor TSP ranged between 20 and 363 $\mu g/m^3$ for all monitoring days and between 27.5 and 129 $\mu g/m^3$ on days of indoor monitoring. Indoor TSP and respirable suspended particle (RSP) ranges were 5.7 to 68.5 $\mu g/m^3$ and 0.1 to 49.7 $\mu g/m^3$, respectively, and were correlated with indoor cigarette smoking but not gas-stove use.

In a preliminary analysis, O_3 and TSP levels were negatively correlated with peak flow, after correction for season and other pollutants. In a multivariate analysis of variance, controlling for person-days of observation, meteorologic factors, CO, NO_2, and TSP, a significant effect of O_3 on peak flow remained ($p < 0.001$). A significant interaction of O_3 with TSP was also observed (z-scores more negative than predicted by an additive model at high O_3 and TSP levels). In multiple regression analyses, the z-scores for person-days with maximum hourly O_3 level and mean O_3 level of at least 0.08 ppm were statistically significant ($p < 0.007$ and $p < 0.0001$, respectively). These scores represented decreases in mean peak flow of 12.2 percent and 14.8 percent, respectively. These changes were significantly different ($p < 0.05$) from changes reported in previously published data (Lebowitz et al., 1982b) on normal day-to-day variation in another, comparable group of children.

Lebowitz et al. (1983, 1985) and Lebowitz (1984) observed a consistent short-term effect of ambient ozone exposure on peak flow. The quantitative usefulness of the study, however, for standard setting is limited by several factors. Sample sizes were small in relation to the number of covariates. The fixed-station aerometric data employed did not allow quantitation of individual ambient pollution exposures. Likewise, since the time spent indoors and outdoors was not measured in the children, the proper relative weights of indoor and outdoor pollution measurements could not be determined for quantitation of exposure.

Selwyn et al. (1985) studied changes in ambient O_3 concentrations in relation to changes in the pulmonary function of healthy adults after vigorous outdoor exercise. From May through October 1981, 24 local residents ran three miles twice a week between 4:30 and 6:30 PM at a track near Houston, Texas. Subjects kept their heart rates between 75 and 90 percent of heart rate during maximal oxygen consumption. Levels of O_3, SO_2, NO_2, CO, temperature, and relative humidity (rh) were measured continuously beside the track. For each run, a subjects' O_3 exposure was considered to be the time-weighted 15-min average of the maximum O_3 concentrations measured during the run. Average inhalable particulate levels were obtained every 12 hr. The average O_3 concentration during runs was 92 $\mu g/m^3$ (0.047 ppm), with a range of 8 to 265 $\mu g/m^3$ (0.004 to 0.135 ppm). Temperature averaged 85 degrees F., and rh averaged 62 percent during runs. Subjects performed forced expiratory maneuvers (FVC, FEV_1, $FEF_{25-75\%}$, and $FEF_{0.2-1.2}$) before and 15 min after each run. Changes in the pulmonary function measures (calculated as post-run minus pre-run values) were regressed against O_3 concentration, with adjustment for temperature and rh. In these regressions, most lung function changes were negatiavely associated with O_3 concentration, but the coefficients for O_3 were not statistically significant at $p = 0.05$.

11.3.1.4 Aggravation of Existing Respiratory Diseases. A number of studies have examined the effects of photochemical oxidants on symptoms and lung functions of patients with asthma, chronic bronchitis, or emphysema. Most of the earlier studies were evaluated in the 1978 EPA criteria document for ozone and other photochemical oxidants (U.S. Environmental Protection Agency, 1978). The results of these as well as more recent studies are summarized in Table 11-5.

For 10 weeks from July to September 1976, Zagraniski et al. (1979) followed 82 patients with asthma or hay fever (patient group) and 192 healthy telephone company employees (worker group) in New Haven, CT. Subjects were asked to

TABLE 11-5. AGGRAVATION OF EXISTING RESPIRATORY DISEASES BY PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.2-0.7 max 1-hr/day 0.20-0.53 max 1-hr/day	Oxidant Ozone	Effects of air filtration on pulmonary function of 47/66 subjects with emphysema staying for variable times in a Los Angeles hospital during a 3½ yr period in the late 1950's; daily maximum hourly concentrations of oxidant, O_3, NO, NO_2, SO_2, and CO by LA-APCD.	Improved lung function in emphysematous subjects staying in the filtered room for ≥40 hr; lack of control for smoking and other pollutants.	Motley et al., 1959[a]
0.13 median	Oxidant	Daily records of the times of onset and severity of asthma attacks of 137 asthmatics residing and working in Pasadena, California between September 3 and December 9, 1956; daily maximum hourly average oxidant levels (KI) from LA-APCD.	Of the 3435 attacks reported, <5% were associated with smog and most of these occurred in the same individuals; time-lagged correlations were lower than concurrent correlations; mean number of patients having attacks on days >0.25 ppm was significantly higher than days <0.25 ppm.	Schoettlin and Landau, 1961[a]
(Not reported)	Oxidant	Effects of community air pollution, occupational exposure to air pollution, and smoking on armed forces veterans with chronic respiratory disease in the Los Angeles Basin between August and December 1958; total oxidant (KI) measured at the site.	No statistically significant effect of air pollution on respiratory function or symptoms.	Schoettlin, 1962[a]
≤0.42 peak (undefined)	Oxidant	Longitudinal study of the effects of environmental variables on pulmonary function of 31 patients with chronic respiratory disease (predominantly emphysema) in a Los Angeles hospital over a period of 18 months; total oxidants (KI), O_3, NO, NO_2, CO, PM, and environmental conditions monitored at a station ½ mile upwind from the hospital.	No consistent pattern of response to episodes of high pollution exposure; possibility of selective sensitivity in some subjects. Unknown measurement method for oxidants. This was only a preliminary study.	Rokaw and Massey, 1962[a]
≤0.2 peak (undefined)	Oxidant	Effects of air filtration on pulmonary function of 15 patients with moderately severe COLD in a Los Angeles County Hospital between July 1964 and February 1965; total oxidant (KI), NO, and NO_2 monitored five times daily.	Raw decreased and P_aO_2 increased in both smokers and nonsmokers after 48 hr in the filtered room. Decreases in Raw were more strongly related to oxidants than NO_2 or NO; however, study lacks rigorous statistical treatment. Questionable effects of smoking and other pollutants.	Remmers and Balchum, 1965[a]; Balchum, 1973; Ury and Hexter, 1969[a]
0.09-0.37 maxima (undefined)	Ozone	Daily diaries for symptoms and medication of 45 asthmatics (aged 7-72 yr) residing in Los Angeles from July 1974 to June 1975; daily average concentrations of O_3, NO, NO_2, SO_2, and CO by LA-APCD within the subjects' residential zone.	No significant relationship between pollutants and asthma symptoms; increased number of attacks at >0.28 ppm in a very small number of subjects; other factors such as animal dander and other pollutants may be important.	Kurata et al., 1976

TABLE 11-5 (continued). AGGRAVATION OF EXISTING RESPIRATORY DISEASES BY PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
(Not reported)	Ozone	Daily log for symptoms, medication, and hospital visitation of 80 children with asthma (aged 8-15 yrs) in the Chicago area during 1974-1975; air quality data on SO_2, CO, PM; partial data for O_3, pollen and climate.	Bad weather and high levels of SO_2, CO, and PM exerted a minor influence on asthma, accounting for only 5-15% of the total variance; high levels of O_3 increased both the frequency and severity of asthmatic attacks; pollen density in fall, and winter temperature variations had no influence. No exposure data given for quantitative treatment.	Khan, 1977
0.004-0.235 max 1-hr	Ozone	Daily symptom rates in 82 asthmatic and allergic patients compared to 192 healthy telephone company employees in New Haven, CT from July to September 1976; average maximum hourly levels of O_3 and average daily values for SO_2, TSP, $SO_4^=$, pollen, and weather were monitored witin 0.8 km of where the subjects were recruited.	Maximum oxidants associated with increased daily prevalence rates for cough, eye, and nose irritation in heavy smokers and patients with predisposing illnesses; pH of particulate was also associated with eye, nose, and throat irritation while suspended sulfates were not associated with any symptoms. Questionable exposure assessment, use of prevalence rather than incidence data, lack of correction for auto regression, and possible bias due to high dropout rates limit the usefulness of this study for developing quantitative exposure-response relationships.	Zagraniski et al., 1979[b]
<0.21 max 1-hr/day	Ozone	Longitudinal study of daily health symptoms and weekly spirometry in 286 subjects with COLD in Houston, TX between July and October 1977 ("Houston Area Oxidants Study"); daily maximum hourly concentration of O_3 measured at site nearest the subjects' residential zone; partial peak levels of PAN, NO_2, SO_2, HC, CO, PM, allergens, and temperature at some monitoring sites.	Increased incidence of chest discomfort, eye irritation, and malaise with increasing concentrations of PAN; increased incidence of nasal and respiratory symptoms and increased frequency of medication use with increasing O_3 concentration; FEV_1, and FVC decreased with increasing O_3 and total oxidant (O_3 + PAN) concentration. Questionable exposure assessment and statistical analysis, weak study design, and lack of control for confounding variables limit the usefulness of this study for developing quantitative exposure-response relationships.	Johnson et al., 1979[b]; Javitz et al., 1983[b]

TABLE 11-5 (continued). AGGRAVATION OF EXISTING RESPIRATORY DISEASES BY PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.03-0.15 medians at 6 sites	Oxidant	Statistical analysis (repeated-measures design) of CHESS data on daily attack rates for juvenile and adult asthmatics residing in six Los Angeles area communities for 34-week periods (May-December) during 1972-1975; daily maximum hourly averages for oxidants (KI) by LA-APCDs, 24-hr averages for TSP, RSP, SO_x, NO_x, SO_2, and NO_2 by EPA, and meteorological conditions were monitored within 1 to 8 miles of homes in each community.	Daily asthma attack rates increased on days with high oxidant and particulate levels and on cool days; presence of attack on the preceding day, day of week, and day of study were highly significant predictors of an attack; questionable exposure assessment including lack of control for medication use, pollen counts, respiratory infections, and other pollutants and possible reporting biases limit the usefulness of this study for developing quantitative exposure-response relationships.	Whittemore and Korn, 1980[a]
0.038-0.12 max 1-hr/day	Ozone	As part of a community population sample of 117 families from Tucson, AZ, daily symptoms, medication use, and ventilatory function were studied in adults with asthma, allergies, or airway obstructive disease (AOD) for an 11-month period in 1979 and 1980; 1-hr maximum concentrations of O_3 (CHEM), NO_2, CO, and daily levels of TSP, allergens, and weather variables were monitored at central stations within ½ mile of each cluster of subjects.	In adults with AOD, O_3 and TSP were significantly associated with peak flow (Wright Peak Flow Meter) after adjusting for covariables; however, no interaction for O_3 + TSP with peak flow. In adults with asthma, O_3 was not significantly related to peak flow after adjusting for covariables; however, there was a significant interaction for O_3 + temperature with peak flow and symptoms. Small number of subjects actually studied and interaction with other environmental conditions limit the quantitative interpretation of these studies.	Lebowitz et al., 1982a[b], 1983[b]; 1985[b]; Lebowitz, 1984[b]
0.001-0.127 max 1-hr	Ozone	Association of O_3 exposure with the probability of asthma attacks in subjects (aged 7-55 yrs) residing in two Houston communities during May-Oct., 1981. Maximum hourly averages for O_3 (CHEM), NO_2, CO, SO_2, temperature, and rh; daily 12-hr averages for fine (<2.5 μ) and coarse (2.5-15 μ) particles, aldehydes and aeroallergens; daily 24-hr averages for TSP. Fixed-rate monitoring within 2.5 miles of subjects residence; time-specific individual exposure estimates were developed using aerometric data and activity data for individuals.	Increased probability of an asthma attack was associated with the occurrence of a previous attack and with exposure to increased O_3 concentration and decreased temperature; only suggested importance of pollen. Magnitude of the O_3 effect varies with the levels of the other covariates; however, other stimuli may be involved including SO_2 and particulates which were not analyzed. In addition, uncertainties about the use of a logistic regression model limits the usefulness of this study for developing quantitative exposure-response relationships.	Holguin et al., 1985[b]; Contant et al., 1985[b]

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[a] Reviewed in U.S. Environmental Protection Agency (1978).

[b] See text for discussion.

complete daily symptom diaries, which were distributed and collected weekly. The groups differed in their distributions of age, gender, smoking history, and job type, though these variables, as well as ethnic group, appear to have been controlled in the statistical analysis.

Air pollution was monitored at two downtown sites 1.2 km apart. Concentrations of SO_2, TSP, sulfates (from dried glass-fiber filters), and O_3 (by chemiluminescence) were measured, as was the pH of filter samples (using KCl in distilled water). Previously measured NO_2 and CO levels had been low. Daily maximum temperature was treated as a covariate. Maximum hourly O_3 levels ranged from 8 to 461 $\mu g/m^3$ (0.004 to 0.235 ppm) and averaged 157 $\mu g/m^3$ (0.08 ppm). Eight- and 24-hour mean TSP levels were 83 and 73 $\mu g/m^3$, respectively. The 24-hour mean SO_4 level was 12.5 $\mu g/m^3$. Ozone and SO_4 peaks often occurred simultaneously. Reported outdoor exposure, working, and home conditions were judged to be equivalent for most subjects for most pollutants.

The data were analyzed by pairwise correlation and multiple regression, in which daily symptom prevalence was the dependent variable. Few associations of symptoms with pollution levels were observed. The maximum hourly O_3, however, was positively and significantly correlated ($p < 0.05$) with cough and nasal irritation in heavy smokers, with cough in hay fever patients, and with nasal irritation in asthmatics. In multiple regression analysis, the O_3 level was associated with cough and eye irritation in heavy smokers, and with cough in hay fever patients. Cough frequency increased linearly with maximum hourly O_3 levels, particularly in heavy smokers and in subjects with pre-existing illness. Filter pH was negatively associated with eye, nose, and throat irritation in most groups. Pollen was positively associated with sneezing in hay fever patients. Sulfate levels were not consistently associated with symptoms.

Although it suggests a relationship between ambient ozone exposure and symptom prevalence, the study does not allow quantitative inference as to pollution exposures of individual subjects, largely because the distances between monitoring sites and respective homes and workplaces were not reported. Also, interpretation is limited by the fact that the dependent variable, symptom prevalence, ignores the potential dependence of present day's symptom on previous day's symptoms. Use of incidence, or adjustment for previous day's symptoms, would have been more appropriate than use of prevalence. Furthermore, the regression models were not clearly described, and thus the appropriateness of statistical corrections can not be assessed with confidence.

Whittemore and Korn (1980) applied multiple logistic regression analysis to asthma panel data collected in six southern California communities during 1972 through 1975. The panels were recruited by the U.S. Environmental Protection Agency (EPA) as part of the Community Health Environmental Surveillance System (CHESS). Subjects with physician-diagnosed, active asthma kept symptom diaries in which they were asked to report the presence or absence of an asthma attack each day for 34 weeks. Each diary contained information for one week; diaries not returned after 16 days were excluded from analysis. The EPA data sets used have undergone quality control to ensure accurate coding of health responses. There were 16 period- and community-specific panels. In selecting panelists, preference was given to prospective subjects reporting frequent asthma attacks; local physicians were consulted before final selection.

Concentrations of TSP, RSP, SO_4, and NO_3 were measured by EPA in each community. Because a large proportion of EPA ozone measurements were missing, total oxidant measurements made by the Los Angeles Air Quality Control District were used instead. Measurements of NO_2 and SO_2 were not used in data analysis because many such measurements were missing. The average distance between subjects' homes and monitoring stations was 3 miles (range 1 to 8 miles). The aerometric data were arranged into 24-hour periods (midday to midday). Daily maximum hourly oxidant levels were used in analysis; panel-specific medians of these ranged from 0.03 to 0.15 ppm. Because RSP, SO_4, and NO_3 were highly correlated with TSP, TSP was the only particulate pollutant included in analysis.

Logistic regression analysis was applied to data from 444 person-periods, 231 male and 213 female. Seventy-two percent of the males' reporting periods were supplied by males under 17 years old; the corresponding percentage of females'reporting periods was 44 percent. It was possible for an individual's data to be analyzed more than once, since some asthmatics participated in more than one panel. The dependent variable was the individual's presence or absence of an asthma attack on a given day. Independent variables were the same day's oxidant and TSP levels, minimum temperature, relative humidity, average windspeed, day of study, and day of week, as well as the individual's presence or absence of an asthma attack on the previous day (autocorrelation variable).

Present day's attack status was most closely associated with the autocorrelation variable, and was also significantly associated with all pollution and weather variables except windspeed. The results suggested high inter-individual variability in response to environmental and meteorologic factors.

The model estimated that a panelist having a baseline attack probability of 0.10 following an attack-free day and a probability of 0.41 on the day after an attack day would have these probabilities raised to 0.13 and 0.44, respectively, if the oxidant level increased by 0.2 ppm. The model also estimated an increase of less than 0.01 when the oxidant level rose by 0.1 ppm.

The Whittemore and Korn (1980) analysis suggests an effect of ambient oxidants on asthma attack rate. The analysis also offers the major advantages of adjusting for previous day's status and confining the individual's model-estimated attack probability to the realistic range of zero to one. These results cannot, however, be considered quantitative. Oxidant measurements, not ozone measurements, were used, and some subjects' homes were distant from aerometric sites. The independent variable was a subjective measure, subject to potential bias. Information on relevant covariates, such as daily medication use, emotional stress, exercise level, acute respiratory infection, and other environmental pollutants and pollen counts, was not collected.

Lebowitz et al. (1982a, 1983, 1985) and Lebowitz (1984) conducted serial studies of Tucson, AZ, adults with asthma, with reported chronic symptoms of airway obstructive disease (AOD), with reported allergies, and without reported symptoms. Subjects were drawn from 117 Anglo-white families from a stratified sample of families in three geographic clusters in a community study population. Subjects were followed for two years with daily symptom and medication diaries and Mini-Wright® peak flow measurements. All families gave information on their home structure, heating, cooling, appliances, and smoking in the household. Telephone checks and visits ensured proper use of diaries, and visits were made to calibrate peak flow meters.

Measurements of air pollutants, pollen, bacilli, fungi, and algae were made in and directly around a random cluster sample of 41 study households (Lebowitz et al., 1984). Pollen and TSP (high-volume samplers) were measured simultaneously in the center of each geographic cluster. Air pollutants were also measured regionally in the Tucson basin (see discussion in previous section for details). Indoor pollution was classified according to indoor smoking and gas-stove use for homes in which indoor monitoring was not done. Indoor particle and pollen concentrations were 100- to 200-fold lower than those outdoors. Scanning electron microscopy showed structural differences between indoor and outdoor dust.

A total of 35 asthmatics provided daily peak flows. For each study group, a given day was included in analysis only if more than five people had provided data on that day. There were 353 such days for asthmatics, 544 for the AOD group, 494 for the allergy group, and 312 for the asymptomatic group. A sex-, age-, and height-specific z-score was computed for each-subject's peak flow. Symptom rates per 100 person-days were calculated separately for asthmatics and non-asthmatics. Asthmatics' attack incidence could not be analyzed because there were only 75 newly incident asthma attacks in 3820 person-days.

The data were analyzed by multivariate analysis of variance and regression analysis. When appropriate, models were adjusted for differences among individuals' person-days of observation. Of the variables considered, smoking was most strongly related to peak flow. In the AOD group, O_3 and TSP were both significantly related to symptoms ($p < 0.01$) after adjustment for gas-stove use, smoking, and relative humidity.

In 23 asthmatics in the geographic cluster where indoor monitoring was most complete, O_3 and temperature had a significant interaction in relation to peak flow; high temperature had an effect when O_3 was low, and O_3 had an effect only at low temperatures. Ozone alone, however, was not independently related to peak flow after adjustment for other pollutants and covariates. There was also a temperature-O_3 interaction on these asthmatics' symptom prevalence; O_3 had an effect (not statistically significant) only in the high-temperature range. Ozone was associated with rhinitis in asthmatics living in homes with gas stoves ($p < 0.015$). Daily medication correlated highly with asthmatics' symptom exacerbations.

The authors speculated that O_3 effects in asthmatics were occurring mainly at levels of 0.052 ppm or greater, but that O_3 appeared to be acting as a surrogate for other oxidants or in conjunction with other environmental factors. These studies included good quality control of health data and unusually extensive environmental monitoring. Like the studies discussed previously, they suggest an effect of ozone in persons with pre-existing respiratory illness. Their results are not truly quantitative, however, largely because sample sizes were often small in relation to the number of covariates, and because not all individuals' pollution exposures were known in detail.

Javitz et al. (1983) reanalyzed a study of 286 persons with asthma, chronic bronchitis, or pulmonary emphysema in Houston, TX (Johnson et al., 1979, unpublished report). Over 114 days from May to October 1977, all subjects were asked to complete daily symptom diaries, and about one-third of the subjects underwent weekly spirometric testing at home. Air pollutants were measured at nine fixed stations in the Houston area. The symptom data were analyzed by logistic regression models, which estimated that the incidence of chest discomfort, eye irritation, and malaise would increase as the PAN concentration increased up to 0.012 ppm. The models also estimated that the incidence of combined nasal symptoms, combined respiratory symptoms, and medication use would increase by 6.0, 3.4, and 5.2 percent, respectively, as the O_3 level increased up to 412 $\mu g/m^3$ (0.21 ppm). The models estimated no increase in any specific nasal or respiratory symptoms with increasing O_3 exposure.

The spirometric data were analyzed by linear regression models, which estimated decreases in FVC and FEV_1 of 2.8 percent and 1.6 percent, respectively, as daily maximum 1-hr O_3 levels rose 412 $\mu g/m^3$ (0.21 ppm). These models estimated somewhat larger decreases in lung function with rising total oxidant (O_3 and PAN) levels. The model-estimated changes in lung function were of questionable statistical significance.

These results suggest a limited effect of ozone on symptoms and lung function in persons with pre-existing lung disease, but substantial limitations in data quality render the results inconclusive. Many aerometric data points were missing, so that individuals' pollution exposures could not be assessed at all confidently. Over one-third of the subjects reported respiratory symptoms on 100 or more days, and over two-thirds reported nasal symptoms on 10 or fewer days. Such skewing of symptom behavior yielded a relatively insensitive test for pollution effects in the study group.

In a preliminary presentation, Holguin et al. (1985) have evaluated the association of O_3 exposure with the probability of an asthma attack in Houston, TX, during May to October 1981. The study population of 51 subjects was carefully selected from individuals residing in the neighborhoods of Clear Lake and Sunnyside. The subjects were medically diagnosed as probable, uncomplicated extrinsic asthmatics, since all had elevated IgE levels, pulmonary function tests consistent with reversible airway disease, and no evidence of other chronic cardiopulmonary disease. Baseline pulmonary function status, however, was not described in detail. Ages of the subjects ranged from 7 to 55 yr but the median age was 13 yr and 41 of the subjects were under 20 yr of age. All subjects completed log forms twice daily providing 12-hr daytime (7 a.m. to 7 p.m.) and 12-hr nighttime (7 p.m. to 7 a.m.) records of hourly symptoms, activities, and location. Pulmonary function measurements of peak flow were also made during the morning and evening reporting times using a Mini-Wright® peak flow meter. Symptoms, medication use, and peak flow data were examined for patterns that fit the clinical description of asthma and that represented deviations from an individuals' baseline profile. Using this information, a specific definition of an asthma attack was derived for each subject.

Fixed-site monitors within 2.5 miles of the subjects residences in each of the two neighborhoods provided: maximum hourly averages for O_3 (CHEM), NO_2, CO, SO_2, temperature, and relative humidity (rh); daily 12-hr averages for fine (<2.5 μm MMAD) and coarse (2.5-15 μm MMAD) particles, aldehydes, and aeroallergens; and daily 24-hr averages for total suspended particulates. Mobile monitoring of indoor/outdoor concentrations of the same pollutants was collected in 12 residences for 1 week. Detailed measurements of personal O_3 exposure were also obtained by means of portable monitors in 30 of 51 study subjects. An exposure model that weighted indoor and outdoor location patterns as well as fixed-site values was used to estimate individual exposures to O_3 and other aerometric variables. Over the 12-hr symptom period, the time-weighted 1-hr maximum O_3 concentrations ranged from 2 to 151 $\mu g/m^3$ (0.001 to 0.077 ppm) with a mean concentration of 37 $\mu g/m^3$ (0.019 ppm). Values for the other environmental variables were not reported.

Logistic regression analysis was applied to 42 subjects, each with more than five attacks. The analysis adjusted for autocorrelation of present day's attack probability with the attack probability on the previous day. Regression coefficients were found to be significantly related to a previous attack, to increasing O_3 concentration, and to decreasing ambient temperature. Elevated concentrations of pollen in September and October increased the probability of an attack in some asthmatics, but this was not statistically significant for the group. There was no association between attack probability and NO_2 or rh.

The utilization of a time-weighted exposure model, employing data from fixed-site as well as mobile monitors, provides an unusually good estimate of actual exposures. Personal exposure data, however, were used to assess the validity of the estimates of individual exposures determined by the model but were not used in the development of the exposure estimate model itself. There are still some uncertainties associated with this approach since results from this comparison indicated that exposure estimates obtained from the model underestimated actual personal exposures by approximately 10 ppb (Contant et al., 1985).

The data analysis by Holguin et al. (1985) provides a means of estimating the increasing probability of an asthma attack on the basis of a previous attack, a 40 ppb increase in O_3, an 8°C increase in ambient temperature, and a combination of these factors. Although the authors estimate the increased attack probabilities associated with incremental O_3 increases from given baseline probabilities, it would be difficult to quantitate these probabilities at any given O_3 concentration since the magnitude of the effect varies as the levels of the other covariates vary. While confounding variables such as NO_2, pollen, and rh were taken into account, other pollutants such as SO_2, total suspended particulates, and inhalable particles (<15 µm MMAD) were not considered in the analysis. The role of other pollutants, particularly the fine inhalable particles, in combination with O_3, temperature, and pollen needs to be evaluated before the results of this study can be used quantitatively.

11.3.1.5 Incidence of Acute Respiratory Illness. Table 11-6 describes studies relating oxidant levels with the incidence of acute respiratory illnesses. These studies, however, did not meet the criteria necessary for developing quantitative exposure-response relationships for ambient oxidant exposures.

11.3.1.6 Physician, Emergency Room, and Hospital Visits. Earlier studies reviewed in the 1978 EPA criteria document for ozone and other photochemical oxidants (U.S. Environmental Protection Agency, 1978) were not able to relate oxidant concentrations to hospital admission rates or clearly separate oxidant effects from effects of other pollutants (Table 11-7). The effects of social factors, which produce day-of-week and weekly cyclical variations, and holiday and seasonal variations, were rarely removed (and then with possible loss of sensitivity). Relating time of visit to time of exposure was also very difficult. Studies of visits to medical facilities in the United States usually lack appropriate denominators since data on the number of individuals at risk are generally not available and the catchment area (total population) is unknown. In addition, with the increased use of the emergency room as a family practice center, visits are becoming less associated with acute exposure or attack than they once were. Also, emergency room data, like hospital record data, often lack information on patients' smoking habits, ethnic group, social class, occupation, and even other medical conditions.

Whether changes in hospital use reflect changes in either illness experience or illness perception and behavior is still uncertain. People may behave differently according to individual perceptions of environmental challenges. The response of the medical-care system is also determined by several factors, including insurance and availability of physicians, beds, and services (Bennett,

TABLE 11-6. INCIDENCE OF ACUTE RESPIRATORY ILLNESS ASSOCIATED WITH PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
≤0.23 avg conc 10 a.m.-3 p.m.	Oxidant	Absentee rates from two elementary schools in Los Angeles throughout the 1962-63 school year; oxidant (KI) concentrations measured by LA-APCD within 2-4.5 miles from each school.	Absence rates were highest during the winter when oxidant levels were lowest; no consistent association between oxidant level and absenteeism. Other pollutants were not considered.	Wayne and Wehrle, 1969[a]
0.08-0.23 max 1-hr/day	Oxidant	Retrospective study on the incidence and duration of influenza-like illness from December 1968 to March 1969 among 3500 elementary school children residing in five Southern California communities.	No relationship between photochemical oxidant gradient and illness rates during an influenze epidemic occurring in a low-oxidant period; all the communities had similar levels. Other pollutants were not considered.	Pearlman et al., 1971[a]
(Not reported)	Oxidant	Health service visits for respiratory illness in students at five Los Angeles and two San Francisco colleges during the 1970-71 school year peak oxidant and mean SO_2, NO_2, NO, NO_x, CO, HC, PM, and weather variables were monitored within 5 miles of each university.	Pharyngitis, bronchitis, tonsilitis, colds, and sore throat associated primarily with oxidant, SO_2, and NO_2 levels on same day and on 7 preceding days; stronger associations in Los Angeles than in San Fransicso.	Durham, 1974[a]
0.066 and 0.079 avg of daily maxima ≤0.195 maximum (undefined)	Oxidant	Health insurance records from two locations in Japan during July-September 1975; maximum oxidant and SO_2 levels and weather variables were monitored daily.	No relationship between oxidant levels and new acute respiratory diseases. Other pollutants beside SO_2 were not considered.	Nagata et al., 1979[a]

[a] Reviewed in U.S. Environmental Protection Agency (1978).

TABLE 11-7. HOSPITAL ADMISSIONS IN RELATION TO PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.11 and 0.28 avg max 1-hr during low and high periods, respectively.	Oxidant	Comparison of admissions to Los Angeles County Hospital for respiratory and cardiac conditions during smog and smog-free periods from August to November 1954.	No consistent relationship between admissions and high smog periods; however, statistical analyses were not reported.	California Department of Public Health, 1955[a], 1956[a], 1957[a]
0.12 avg conc 6 a.m.-1 p.m.	Oxidant	Respiratory and cardiovascular admissions to Los Angeles County Hospital for residents living within 8 miles of downtown LA between August and December, 1954.	Inconclusive results; partial correlation coefficients between total oxidants and admissions were variable. Method of patient selection was not given. Other pollutants were not considered.	Brant and Hill, 1964[a]; Brant, 1965
(Not reported)	Oxidant	Admissions of Blue Cross patients to Los Angeles hospitals with >100 beds between March and October 1961; daily average concentrations of oxidant, O_3, CO, SO_2, NO_2, NO, and PM by LA-APCDs.	Correlation coefficients between admissions for allergies, eye inflammation, and acute upper and lower respiratory infections and all pollutants were statistically significant; correlations between cardiovascular and other respiratory diseases were significant for oxidant, O_3, and SO_2; significant positive correlations were noted with length of hospital stay for SO_2, NO_2, and NO_x. Correlations were not significant for temperature and relative humidity or for pollutants with other disease categories.	Sterling et al., 1966[a], 1967[a]
(Not reported)	Oxidant	Admissions for all adults and children with acute respiratory illness in 4 Hamilton, Ontario hospitals during the 12 months from July 1, 1970 to June 30, 1971; city-average pollution monitoring for Ox(KI), SO_2, PM, COH, CO, NO_x, HC, and temperature, wind direction and velocity, relative humidity, and pollen.	Correlation between number of admissions and an air pollution index for SO_2 and COH; negative correlation between temperature and admissions. No correlation was found with concentrations of Ox, CO, HC, and NO_x or with pollen, relative humidity, wind direction, and velocity.	Levy et al., 1977
(Not reported)	Ozone	Emergency room visits for cardiac and respiratory disease in two major hospitals in the city of Chicago during April 1977 to April 1978; 1-hr concentrations of O_3, SO_2, NO_2, NO, and CO from an EPA site close to the hospital, 24-hr concentrations of TSP, SO_2, and NO_2 from the Chicago Air Sampling Network.	No significant association between admissions for any disease groups and O_3, CO, or TSP; SO_2 and NO accounted for part of the variation of ER visits for respiratory and cardiovascular admissions. Questionable study design and analysis including lack of control for confounding and weak exposure assessment.	Namekata et al., 1979[b]

TABLE 11-7 (continued). HOSPITAL ADMISSIONS IN RELATION TO PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.07 and 0.39 avg max 1-hr during low and high periods, respectively	Ozone	Emergency room visits and hospital admissions for children with asthma symptoms during periods of high and low air pollution in Los Angeles from August 1979 to January 1980; daily maximum hourly concentrations of O_3, SO_2, NO, NO_2, HC, and COH; weekly maximum hourly concentrations of $SO_4^=$ and TSP; biweekly allergens and daily meterological variables from regional monitoring stations.	Asthma positively correlated with COH, HC, NO_2, and allergens on same day and negatively correlated with O_3 and SO_2; asthma positively correlated with NO_2 on days 2 and 3 after exposure; correlations were stronger on day 2 for most variables; nonsignificant correlations for $SO_4^=$ and TSP. No indication of increased symptoms or medication use during high pollution period; however, peak flow decreased (no differentiation of pollutants). Factor analysis suggested possible synergism between NO, NO_2, rh, and windspeed; O_3, SO_2, and temperature; and allergens and windspeed. Presence of confounding variables, lack of definitive diagnoses for asthma and questionable exposure assessment limit the quantitative interpretation of this study.	Richards et al., 1981[b]
0.03 and 0.11 avg max 1-hr for low and high areas, respectively	Oxidant	Daily hospital emergency room admissions in four Southern California communities during 1974-1975. Maximum hourly average concentrations of oxidant, NO_2, NO, CO, SO_2, COH; 24-hr average concentrations of PM and $SO_4^=$; and daily meteorological conditions from monitoring sites ≤ 8 km from the hospitals.	Admissions associated with oxidant in Azusa (the highest oxidant pollution), $SO_4^=$ in Long Beach and Lennox but not Riverside (the highest sulfate pollution), and with temperature in all locations. Lack of sufficient exposure analysis and subject characterization limit the quantitative use of this study.	Goldsmith et al., 1983[b]
0.03-0.12 avg of max 1-hr/day for 15 stations	Ozone	Admissions to 79 acute-care hospitals in Southern Ontario for the months of January, February, July, and August in 1974, 1976-1978. Hourly average concentrations of particulate (COH), O_3, SO_2, NO_2, and daily temperature from 15 air sampling stations within the region.	Excess respiratory admissions associated with SO_2, O_3, and temperature during July and August with 24 and 48 hr lag; only temperature was associated with excess respiratory admissions and total hospital admissions for January and February. Lack of sufficient exposure analysis limits the quantitative use of this study.	Bates and Sizto, 1983[b]

[a] Reviewed in U.S. Environmental Protection Agency (1978).

[b] See text for discussion.

1981; Ward and Moschandreas, 1978). Artifacts may arise from changing definitions of classifications and varying diagnostic or coding practices as well. Another frequent problem is that repeated admissions or attendance by a small number of patients can cause tremendous distortions in the data (Ward and Moschandreas, 1978). Furthermore, interpretation of hospital admissions data is hindered because hospital statistics often lack reliability and validity such that determining disease incidence is difficult; insufficient clinical data are available for diagnostic classification and grading of severity; and a number of potential subclassifications of patients may require separation and attention in the analysis (Ward and Moschandreas, 1978).

Namekata et al. (1979) found no significant association between O_3 levels and emergency room visits for cardiac and respiratory diseases in two Chicago hospitals during 1977-1978. This study, however, must be considered inadequate because information collected from the medical records was insufficient for identifying sources of variability in the data and for controlling confounding factors of the types noted above. In addition, the O_3 data were insufficient and incomplete and the linear models used could not determine effect levels of the pollutant.

Richards et al. (1981) evaluated the relationship between asthma emergency room visits and hospital admissions and indices of air pollution, meteorological conditions, and airborne allergens. Questionnaire data were obtained on all children presenting to the Emergency Room of Childrens Hospital of Los Angeles for symptoms associated with asthma during a 6-month period (August 1, 1979 to January 31, 1980), encompassing both high and low periods of air pollution. Air pollution and meteorological data were obtained from monitoring stations located in the geographical area and weighted according to the density of patients residing near the monitoring stations. The weighted averages were used to calculate an average exposure representative of the entire geographical area. Univariate correlation analyses demonstrated a number of positive and negative correlations of asthma with air pollutants; however, when asthma morbidity was regressed on the combined factor scores, 30 percent of the total variation could be explained by air pollution or meteorological conditions. Other variables such as restriction of outdoor activity or exposure to other irritants that were not measured could also have affected asthma morbidity. In addition, this study suffers from many of the problems enumerated above. There was difficulty establishing a definitive diagnosis of asthma retrospectively in the patients, inadequate exposure assessment, no clear differentiation of O_3 effects from the effects of other pollutants, and the presence of multiple confounding variables.

Goldsmith et al. (1983) studied emergency room visits in four Southern California communities (Long Beach, Lennox, Azusa, and Riverside) during 1974-1975. Logbook data on total admissions were taken from two hospitals in each of the first three communities and from three hospitals in the fourth. The hospitals were $\leq$ 8 km from Southern California Air Quality Management District stations monitoring TSP, O_x, CO, NO, NO_2, SO_2, sulfate (SO_4), and coefficient of haze (COH). Catchment areas and air monitoring data for residential and work sites were unknown for the subjects included in the study. The data were adjusted for day-of-the-week and long-term trends, but not for seasonal trends. Maximum hourly averages of oxidants and temperature were reported to be associated with daily admissions in the high-oxidant area (Azusa) after correction for other variables using correlation coefficients from path analysis (although the more complete path analysis explained less variance than the standard regression model). Unfortunately, the lack of population denominators and characteristics, the lack of admission characteristics, and poor characterization of exposure seriously limit the use of these findings.

Bates and Sizto (1983) studied admissions to all 79 acute-care hospitals in Southern Ontario, Canada (i.e., the whole catchment area of 5.9 million people) for the months of January, February, July, and August in each of 6 years (1974, 1976-1978, and 1979-1980). Air pollution data for CO, NO_2, O_3, and particles (COH) were obtained from 15 stations located mostly along the prevailing wind direction. Temperature was controlled. In July and August, highly significant assocations (Pearson r, 1-tailed, $P \leq 0.001$) were found between excess (percent deviations from day-of-week and seasonal means) respiratory admissions and average maximum hourly SO_2 and O_3 concentrations, and temperature (with 24- and 48-hr lags between the variables). Nonrespiratory admissions showed no relation to pollution. Temperature was independently important (-5.3°C average on winter days in study). Admissions, and admission correlations with pollutants, were consistent from year to year. Further analysis showed that asthma was the most significant respiratory problem driving the admissions up, especially in younger people. Bronchitis and pneumonia admissions were not significantly related to pollutants. The authors state that it was difficult to differentiate between the effects of temperature, SO_2, and O_3. With data extended through 1980 (Bates, 1985), however, there is preliminary information that sulfate levels accounted for a high percentage of explained variations for all respiratory complaints, but that ozone was still independently associated with asthma. Since the number of separate people admitted was unknown, a "sensitive" subpopulation could have affected the results. In addition, actual exposure information can only be approximated in this type of study so that only qualitative associations can be drawn between ambient pollutants and morbidity increases in the population.

11.3.1.7 Occupational Studies. Studies of acute effects from occupational exposure are summarized in Table 11-8. These studies did not meet the criteria necessary for developing quantitative exposure-response relationships for ambient oxidant exposures.

11.3.2 Trends in Mortality

The possible association between acute exposure to photochemical oxidants and increased mortality rates has been investigated a number of times (Table 11-9) and the results have been reviewed at length in previous documents (National Research Council, 1977; U.S. Environmental Protection Agency, 1978; World Health Organization, 1978; Ferris, 1978). As yet, no convincing association has been demonstrated between daily mortality and daily oxidant concentrations. High oxidant levels were usually associated with high temperatures that were sufficient to account for any excess mortality found in these studies.

11.4 EPIDEMIOLOGICAL STUDIES OF EFFECTS OF CHRONIC EXPOSURE

Only a few prospective studies of the chronic effects of O_3 exposure are available. These studies are usually concerned with the association of symptoms, lung function, chromosomal effects, or mortality rates and average annual levels of photochemical oxidants; or comparisons of chronic effects in populations residing in low- or high-oxidant areas. The inability to relate chronic effects with chronic exposure to specific levels of pollutants is a major limitation of these studies. In addition, given the long periods of time known to be required for the development of chronic diseases, it is unlikely that any of these studies can be used to develop quantitative exposure-response relationships for ambient oxidant exposures. Further study of well-defined populations over long periods of time is required before any relationship between photochemical oxidants and the progression of chronic diseases can be conclusively demonstrated from population studies.

TABLE 11-8. ACUTE EFFECTS FROM OCCUPATIONAL EXPOSURE TO PHOTOCHEMICAL OXIDANTS

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
(Not reported)	Ozone	Health complaints of workers in a test laboratory of a factory for electric insulators.	Reports of thoracic cage constriction, inspiration difficulty, and laryngeal irritation. Other pollutants were not controlled.	Truche, 1951
0.25-0.80 peaks (undefined)	Ozone	Clinical findings and symptoms in welders using inert gas-shield consumable electrodes in three plants with ozone measured at breathing zones.	Increase in chest constriction and throat irritation at 1-hr concentrations of 0.3 to 0.8 ppm; no complaints or clinical findings below 0.25 ppm. Nitrogen dioxide and total suspended particulate matter were not measured or controlled.	Kleinfeld et al., 1957
0.8-1.7 peaks (undefined)	Ozone	Symptoms in 14 helio-arc welders.	Upper respiratory symptoms in 11 of 14 welders exposed daily to 0.8 to 1.7 ppm ozone, which disappeared with exposure to 0.2 ppm. Nitrogen dioxide was present, but not studied.	Challen et al., 1958
0.2-0.3 means	Ozone	Lung function in seven welders using argon-shield. O_3 measured by rubber cracking.	No changes in function. Nitrogen dioxide was probably present, but not controlled.	Young et al., 1963
0.56-1.28 (interval not specified)	Ozone	Symptoms in welders and nearby workers (controls) ages 25-35, with less than 5 years employment.	More frequent complaints of respiratory irritation, headache, fatigue, and nosebleeds in welders; exams were normal. Carbon monoxide and nitrogen dioxide were below permissible levels. Total suspended particulate matter was not studied.	Polonskaya, 1968
0.01-0.36 peaks (undefined)	Ozone	Illness in 61 welders, 63 pipefitters, 61 pipecoverers, and 94 new pipefitters, measured by questionnaires, pulmonary function, partial physicals, and X-rays.	Lung function obstruction in smokers in first two groups; third group had restrictive function. Otherwise, no differences were observed. Many pollutants were also involved.	Peters et al., 1973

TABLE 11-8 (continued). ACUTE EFFECTS FROM OCCUPATIONAL EXPOSURE TO PHOTOCHEMICAL OXIDANTS

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.05-0.5 workshift avg	Ozone	Pulmonary function in workers in a plastic bag factory (31 exposed and 31 controls of same age, height, smoking habits).	Decreased expiratory flow in 8 of 31 subjects during workshift. Lower flows in exposed smokers than control smokers. Acute changes to acetylcholinesterase, peroxidase, and lactate dehydrogenase. Other pollutants, including formaldehyde (0.18 to 0.20 ppm) were not controlled.	Fabbri et al., 1979
0.16-0.29 workshift avg	Ozone	Extrapulmonary effects in 33 workers in a plastic bag factory.	Altered serum enzyme levels in 22 subjects; peroxidase activity of peripheral leucocytes increased at the end of the workshift but returned to normal after a holiday.	Sarto et al., 1979a,b
0.08 workshift avg <1.0 peaks (undefined)	Ozone	Health effects in male German metallurgical plant workers, as measured by questionnaire, absenteeism, insurance records, vital capacity measures, plethysmographic measures, blood pressure, and airway resistance. Ozone, nitrogen oxides, and sulfur oxides were sampled.	Group exposed to high ozone had more absenteeism and more episodes of bronchitis and pneumonia, more cough and phlegm, and higher airway resistance than did controls. However, high total suspended particulate matter levels and temperature-induced volatilized metals obscured effects of ozone.	von Nieding and Wagner, 1980
0.01-0.15 avg personal exposure	Ozone	Changes in immune responses of 30 workers (average age = 34 yr) exposed an average of 4.3 yr to O_3 when compared to a control group of ore miners.	Levels of alpha-1-antitrypsin and transferrin increased after exposure. Comparisons of relative numbers of changes in serum and plasma proteins and in the immunological responses of peripheral lymphocytes in both groups indicates considerable interindividual variability.	Ulrich et al., 1980

TABLE 11-9. DAILY MORTALITY ASSOCIATED WITH EXPOSURE TO PHOTOCHEMICAL OXIDANT POLLUTION

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
≤1.0 peak (undefined)	Oxidant	Relationship between daily concentrations of photochemical oxidants and daily mortality among residents of Los Angeles County aged 65 yrs and over the periods August-November 1954 and July-November 1955.	Heat had a significant effect on mortality; no consistent association between mortality and high oxidant concentrations in the absence of high temperature.	California Department of Public Health, 1955[a], 1956[a], 1957[a]
≤0.38 max 1-hr(?)/day	Oxidant	Data extended to include the period from 1956 through the end of 1959.		Tucker, 1962
(Not reported) 0.10-0.67 (undefined) for 180 days of 1955	Oxidant Ozone	Relationship between daily maximum oxidant concentrations and daily cardiac and respiratory mortality in Los Angeles for the periods 1947-1949, August 1953 through December 1954, and January 1955 through September 1955.	Positive relationship between daily maximum oxidant concentrations and mean daily death rates on high-smog vs. low-smog days. Questionable exposure analysis including use of the "SRI smog index."	Mills, 1957a[a],b[a]
(Not reported)	Oxidant	Comparison of daily mortality in two Los Angeles County areas similar in temperature but with different levels of daily maximum and mean oxidant levels (KI); SO_2 and CO concentrations were also measured.	No significant correlations between differences in mortality and differences in pollutant levels.	Massey et al., 1961[a]
0.05-0.23 monthly avgs	Oxidant	Relationship between daily maximum oxidant concentrations (KI) and daily mortality from cardiac and respiratory diseases in Los Angeles for the years 1956 through 1958.	No significant correlations between pollutants and mortality for cardiorespiratory diseases; no correlation for a 1-4 day lag in exposure and mortality.	Hechter and Goldsmith, 1961[a]
(Not reported)	Oxidant	Relationship between daily total mortality from all causes and three Los Angeles heat waves occurring in 1939, 1955, and 1963; comparison with mortality during the same season in 1967 without a heat wave.	High photochemical oxidant concentrations do not augment the effect of high temperature on mortality; however, no statistical relationship was determined between mortality and oxidant exposure.	Oechsli and Buechley, 1970[a]
0.010-0.159 max 1-hr/day	Ozone	Relationship between daily mortality and daily 1-hr maximum concentrations of O_3 in Rotterdam, The Netherlands during the months of July and August of 1974 and 1975.	No significant correlation between O_3 concentration and mortality in the absence of high temperature; no augmentation of mortality due to increased temperature during heat waves.	Biersteker and Evendijk, 1976

[a] Reviewed in U.S. Environmental Protection Agency (1978).

11.4.1 Pulmonary Function and Chronic Lung Disease

Studies of chronic respiratory morbidity are summarized in Table 11-10. While some of these studies (Detels et al., 1979, 1981; Rokaw et al., 1980; Hodgkin et al., 1984) suggest an increase in the prevalence of respiratory symptoms or possibly impairment of pulmonary function in high-pollutant areas, the results do not show any consistent relationship with chronic exposure to ozone or other photochemical oxidants. In addition, as discussed above, these studies are generally limited by insufficient information about individual exposures and by their inability to control for the effects of other environmental factors. They do not provide information useful for quantitative exposure-effect assessment. Thus, to date, insufficient information is available in the epidemiological literature on possible exposure-effect relationships between O_3 or other photochemical oxidants and the prevalence of chronic lung disease. These relationships will need further study.

One of the largest investigations of chronic O_3 exposure has been the series of population studies of chronic obstructive respiratory diseases in communities with different air pollutant exposures, reported by Detels and colleagues of the University of California at Los Angeles (UCLA) (Detels et al., 1979, 1981; Rokaw et al., 1980). The areas studied were characterized by high levels of photochemical oxidants (Burbank and Glendora, CA); high levels of SO_x, particulates, and HCs (Long Beach, CA); and low levels of gaseous pollutants (Lancaster, CA). The prevalence of symptoms was reported to be increased in the residents of the highest-polluted area (Glendora). Lung function was generally better among residents of the low-pollution areas, as indicated by FEV_1, FVC, maximum expiratory flow rates, closing volume, thoracic volume, and airway resistance. Maximal mid-expiratory flow rate, considered to be sensitive to changes in small airways, was similar in the residents of all three areas, while the mean ΔN_2 was slightly higher among residents of the high-pollution areas. Although the results suggest that adverse effects of long-term exposure to photochemical oxidant pollutants may occur primarily in the larger airways, the usefulness of these studies is limited by a number of problems. For example, testing in different communities occurred at different times over a 4-year period. Also, the authors presented no information on such matters as self-selection and migration in and out of these areas.

Additional comparisons between mobile laboratory and hospital laboratory test results did not always show adequate reproducibility. The study populations had mixed ethnic groups, and completion rates were approximately 70 to

TABLE 11-11. PULMONARY FUNCTION EFFECTS ASSOCIATED WITH CHRONIC PHOTOCHEMICAL OXIDANT EXPOSURE

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
≥0.5 peak (unconfirmed)	Oxidant	Comparison of weekly surveys of illness and injury rates between population samples from Los Angeles County and the rest of California during 17 weeks from August through November 1954.	No relationship between incidence of illness and area in the young. Elderly showed some increases in Los Angeles but investigators did not adjust for differences in population density, ethnic characteristics, and socio-economic level. Pollutants other than ozone were also higher.	California Department of Public Health 1955[a], 1956[a], 1957[a]
(Not reported)	Oxidant	Prevalence of illness in survey of 3545 households throughout California. Chronic pulmonary disease studied four times, 1957-1959.	Higher prevalence rates in Los Angeles and San Diego. No quantitative oxidant data. Questionable study design and data analysis.	Hausknecht and Breslow, 1960[a]; Hausknecht, 1962[a]
(Not reported)	Oxidant	Symptoms, measured by questionnaire and ventilatory function, in outdoor telephone workers 40-59 years of age in San Francisco and Los Angeles.	Respiratory symptoms were more frequent in the older age group (50-59 yrs) of Los Angeles but pulmonary function was similar. No differences in symptom prevalence between cities in the younger group (40-49 yrs), although particulate concentrations were about twice as high in Los Angeles. No aerometric data.	Deane et al., 1965[a]; Goldsmith and Deane, 1965[a]
0.07 and 0.12 avg max 1-hr for low and high areas, respectively	Oxidant	Comparison of pulmonary function in nonsmoking Seventh Day Adventists (aged 45-64 yrs) residing in high-oxidant (San Gabriel Valley) and low-oxidant (San Diego) areas of California in January 1970; average maximum oxidant concentrations were obtained from September 1969 and January 1970; TSP, RSP, and SO_2 were also measured.	No significant difference in prevalence of respiratory symptoms or in measurements of pulmonary function; however, the findings are limited by the similarity of annual average ambient levels of oxidants in the two areas.	Cohen et al., 1972[a]
0.15 and 0.33 max 1-hr for the low and high areas, respectively	Oxidant	Respiratory symptoms and function in insurance company workers in Los Angeles and San Francisco during the Spring and Summer of 1973; median concentrations of oxidant, NO_2, SO_2, CO, TSP, and weather were measured from 1969 to 1972 at central-city monitoring stations.	Sex-specific pulmonary function measurements were similar in all tests; no difference in chronic respiratory symptom prevalence between cities. More frequent reports of nonpersistent (<2 years) production of cough and sputum by women in Los Angeles. Different populations and different aerometric characteristics complicate the analysis.	Linn et al., 1976[a]

TABLE 11-13 (continued). PULMONARY FUNCTION EFFECTS ASSOCIATED WITH CHRONIC PHOTOCHEMICAL OXIDANT EXPOSURE

Concentration(s) ppm	Pollutant	Study description	Results and comments	Reference
0.07 and 0.09 annual means of max 1-hr/day for Lancaster and Burbank, respectively	Oxidant	UCLA population studies of the prevalence of symptoms of chronic obstructive respiratory disease (CORD) and of functional respiratory impairment in residents of California communities with differing photochemical oxidant concentrations. Daily maximum hourly average concentrations of oxidant, O_3, NO_x, SO_2, CO, and HC; 24-hr average concentrations of TSP and $SO_4^=$ from regional SCAQMD and CARB monitoring stations within 1 to 3 miles of the subjects residential zone.	Increased prevalence of respiratory symptoms in the residents of high-pollution areas; pulmonary functon tests of small airways showed little or no differences between areas while results of large airway function suggests that long-term exposure to high concentrations of pollutants (oxidants SO_2, NO_2, PM, and HC) may result in measurable impairment. Difficulty in judging ambient pollution exposure and lack of control for confounding environmental conditions migration, smoking history, and occupational exposure restrict the quantative interpretation of these studies.	Detels et al., 1979[a]
0.08, 0.07, and 0.09 annual means of max 1-hr/day for Long Beach, Lancaster, and Burbank, respectively				Rokaw et al., 1980[b]
0.07 and 0.12 annual means of max 1-hr/day for Lancaster and Glendora, respectively				Detels et al., 1981[b]
(Not reported)	Oxidant	Prevalence of respiratory symptoms in nonsmoking Seventh Day Adventists residing for at least 11 yrs in high (South Coast) and low (San Francisco, San Diego) photochemical air pollution areas of California; CARB regional air basin monitoring data for oxidants, NO_2, SO_2, CO, TSP, and SO_4 from 1973 to 1976.	Slightly increased prevalence of respiratory symptoms in high pollution area; after adjusting for covariables, 15% greater risk for COPD due to air pollution (not specific to oxidants); past smokers had greater risk than never smokers; when past smokers were excluded, risk factors were similar. Use of symptoms as risk for COPD without FEV_1 data is questionable. In addition, insufficient exposure assessment and confounding by environmental conditions limit the quantitative use of this study.	Hodgkin et al., 1984
(Not reported)	Oxidant	Respiratory symptoms and function in 360 wives and daughters of shipyard workers in Long Beach, CA compared to a reference population from Michigan.	Increased prevalence of chronic bronchitis, reduced expiratory air flow, and altered gas distribution in the Long Beach cohort; all subjects in this cohort had family exposure [illegible] and 31/238 wives and 8/122 daughters had clinical signs of asbestosis. Questionable effects of smoking and other pollutants; no oxidant exposure data were presented.	Kilburn et al., 1985

[a] Reviewed in U.S. Environmental Protection Agency (1978).

[b] See text for discussion.

79 percent in the three areas. Comparisons of participants with census information were fairly close. Analysis of the comparisons of the three communities for symptoms and pulmonary function results used age- and sex-adjusted data only from white residents who had no history of change of occupation or residence because of breathing problems. Those with occupations that may have involved significant exposure were not necessarily excluded. Analyses were often made by smoking status and compared means or proportions that fell above or below certain levels.

A major difficulty in the analyses is that the exposure data presented are not adequate. Control of migration effects on chronic exposure was insufficient, and recent exposure information was provided only by ambient levels from only one monitor, located as far as 3 mi away. A further problem is that, as in most geographical comparisons, analysis of results assumes no differences by place, date, or season. This assumption is especially important since the study periods in each community were different. Furthermore, over the 4-year period of the study there were many changes, including amounts and types of cigarettes smoked, respiratory infection epidemics, and other undeterminable influences that could have affected the results. Also, the numbers of subjects changed from one report to another and from one analysis to another.

Interpretation of the UCLA lung function data is complicated by the fact that fewer smokers had abnormal lung function than might be expected. Also, some of the tests employed, e.g., flow rates at low lung volumes and single-breath nitrogen tests, require stringent measures to avoid observer bias. It is not clear whether such measures were taken in the UCLA studies.

To test for health effects of air pollution, the investigators often compared the lower ends (three to five standard deviations below the means) of the distributions of the study communities' health measurements. It is very difficult to interpret such comparisons unless the other portions of the distributions are also presented. Also, numbers of cases were sometimes relatively small, and some results, e.g., those of the single-breath nitrogen test, suggested improving lung function with increasing pollution exposure. It is not clear whether covariates were appropriately treated in data analysis. Thus, this work is not sufficiently quantitative for air quality standard-setting purposes.

11.4.2 Chromosomal Effects

The importance of chromosomal damage depends on whether the effect is mutagenic or cytogenetic. For example, translocations and trisomies are im-portant forms of genetic damage, whereas minor chromosomal breakage (such as that associated with caffeine) and chromatid aberrations are of questionable significance. Interest in the existence and extent of chromosomal damage in populations exposed to O_3 derives from *in vitro* cell studies and *in vivo* animal studies (Chapter 9). Findings from *in vivo* human studies are conflicting, but generally negative (Chapter 10).

Chromosomal changes in humans exposed to O_3 have been investigated in four epidemiological studies, none of which found any evidence that O_3 affects peripheral lymphocytic chromosomes in humans at the reported ambient concentrations. For example, Scott and Burkart (1978) studied chromosome lesions in peripheral lymphocytes of students exposed to air pollutants in Los Angeles. In their study of 256 college students, who were followed continuously, chromosomal changes found were almost entirely of the simple-breakage type and were no more numerous than the predicted incidence for a population.

Magie et al. (1982) studied chromosomal aberrations in peripheral lymphocytes of college students in Los Angeles: 209 nonsmoking freshmen at a campus with higher smog levels ($\geq$0.08 ppm O_3; $\geq$160 μg/m^3) and 206 freshmen at a campus with lower smog levels ($<$0.08 ppm O_3; $<$160 μg/m^3). Students were enrolled in the study after completing questionnaires, and were assigned to groups on the basis of campus location and previous residence. Blood samples and medical histories (obtained at the beginning of the school year, in November, in April, and at the beginning of the next school year) were analyzed for chromosome and chromatid aberrations, but no significant effects on chromosomal structure were found in peripheral lymphocytes.

Bloom (1979) studied military recruits before and after welding training. No chromosomal aberrations were seen in peripheral lymphocytes (O_3 levels were negligible and NO_2 was high). Fredga et al. (1982) studied the incidence of chromosomal changes in men occupationally exposed to automobile fuels and exhaust gases in groups of drivers, automobile inspectors, and a control group matched with respect to age, smoking habits, and length of job employment. Chromosome preparations from lymphocytes were made and analyzed by standardized routine methods. Analysis of the data gave no evidence of effects from occupational exposure.

11.4.3 Chronic Disease Mortality

Two studies previously reviewed in the 1978 EPA criteria document for ozone and other photochemical oxidants (U.S. Environmental Protection Agency, 1978) were not able to establish conclusively a relationship between oxidant exposure and mortality from chronic respiratory diseases and lung cancer. Buell et al. (1967) studied mortality rates among members of the California Division of the American Legion for the 5-year period from 1958 through 1962. Long-term residents of Los Angeles County had slightly lower age- and smoking-adjusted lung cancer rates than residents of the San Francisco Bay area and San Diego County. Rates of mortality resulting from chronic respiratory diseases other than lung cancer were higher in Los Angeles than in San Francisco or San Diego, but the rates were highest in the other less urbanized counties. Mahoney (1971) reported higher total respiratory disease mortality rates in inland, downwind sections of Los Angeles than in coastal, upwind sections; however, variables such as smoking, migration within the city, and variation among zones in population density were not considered. In fact, socioeconomic, demographic, and behavioral variables were not fully controlled in either the Buell et al. (1967) or Mahoney (1971) studies and mortality rates were not related to actual pollution measurements.

11.5 SUMMARY AND CONCLUSIONS

Field and epidemiological studies offer a unique view of health effects research because they involve the real world, i.e., the study of human populations in their natural setting. These studies have attendant limitations, however, that must be considered in a critical evaluation of their results. One major problem in singling out the effects of one air pollutant in field studies of morbidity in populations has been the interference of other environmental variables that are critical. Limitations of epidemiological research on the health effects of oxidants include: interference by other air pollutants or interactions between oxidants and other pollutants; meteorological factors such as temperature and relative humidity; proper exposure assessments, including determination of individual activity patterns and adequacy of number and location of pollutant monitors; difficulty in identifying oxidant species responsible for observed effects; and characteristics of the populations such as smoking habits and socioeconomic status.

The most quantitatively useful information of the effects of acute exposure to photochemical oxidants presented in this chapter comes from the field studies of symptoms and pulmonary function. These studies offer the advantage of studying the effects of naturally-occurring, ambient air on a local subject population using the methods and better experimental control typical of controlled-exposure studies. In addition, the measured responses in ambient air can be compared to clean, filtered air without pollutants or to filtered air containing artificially-generated concentrations of O_3 that are comparable to those found in the ambient environment. As shown in Table 11-11, studies by Linn et al. (1980, 1983) and Avol et al. (1983, 1984, 1985a,b,c) have demonstrated that respiratory effects in Los Angeles area residents are related to O_3 concentration and level of exercise. Such effects include: pulmonary function decrements seen at O_3 concentrations of 282 $\mu g/m^3$ (0.144 ppm) in exercising healthy adolescents; and increased respiratory symptoms and pulmonary function decrements seen at O_3 concentrations of 300 $\mu g/m^3$ (0.153 ppm) in heavily exercising athletes and at O_3 concentrations of 341 $\mu g/m^3$ (0.174 ppm) in lightly exercising normal and asthmatic subjects. The light exercise level is probably the type most likely to occur in the exposed population of Los Angeles. The observed effects are typically mild, and generally no substantial differences were seen in asthmatics versus persons with normal respiratory health, although symptoms lasted for a few hours longer in asthmatics. Many of the normal subjects, however, had a history of allergy and appeared to be more sensitive to O_3 than "non-allergic" normal subjects. Concerns raised about the relative contribution to untoward effects in these field studies by pollutants other than O_3 have been diminished by direct comparative findings in exercising athletes (Avol et al., 1984, 1985c) showing no differences in response between chamber exposures to oxidant-polluted ambient air with a mean O_3 concentration of 294 $\mu g/m^3$ (0.15 ppm) and purified air containing a controlled concentration of generated O_3 at 314 $\mu g/m^3$ (0.16 ppm). The relative importance of exercise level, duration of exposure, and individual variations in sensitivity in producing the observed effects remains to be more fully investigated, although the results from field studies relative to those factors are consistent with results from controlled human exposure studies (Chapter 10).

Studies of the effects of both acute and chronic exposures have been reported in the epidemiological literature on photochemical oxidants. Investigative approaches comparing communities with high O_3 concentrations and communities with low O_3 concentrations have usually been unsuccessful, often because

TABLE 11-11. SUMMARY TABLE: ACUTE EFFECTS OF OZONE AND OTHER PHOTOCHEMICAL OXIDANTS IN FIELD STUDIES WITH A MOBILE LABORATORY[a]

Mean ozone concentration µg/m³	ppm	Measurement[b,c] method	Exposure duration	Activity[d] level ($\dot{V}_E$)	Observed effect(s)	No. of subjects	Reference
282	0.144	UV, UV	1 hr	CE(32)	Small significant decreases in FVC (-2.1%), $FEV_{0.75}$ (-4.0%), $FEV_{1.0}$ (-4.2%), and PEFR (-4.4%) relative to control with no recovery during a 1-hr postexposure rest; no significant increases in symptoms.	59 healthy adolescents (12-15 yr)	Avol et al., 1985a,b
300	0.153	UV, UV	1 hr	CE(53)	Mild increases in lower respiratory symptom scores and significant decreases in FEV_1 (-5.3%) and FVC; mean changes in ambient air were not statistically different from those in purified air containing 0.16 ppm O_3.	50 healthy adults (competitive bicyclists)	Avol et al., 1984, 1985c
306	0.156	UV, NBKI	1 hr	CE(38)	No significant changes for total symptom score or forced expiratory performance in normals or asthmatics; however, FEV_1 remained low or decreased further (-3%) 3 hr after ambient air exposure in asthmatics.	48 healthy adults 50 asthmatic adults	Linn et al., 1983; Avol et al., 1983
323	0.165	UV, NBKI	1 hr	CE(42)	Small significant decreases in FEV_1 (-3.3%) and FVC with no recovery during a 1-hr postexposure rest; TLC decreased and ΔN_2 increased slightly.	60 "healthy" adults (7 were asthmatic)	Linn et al., 1983; Avol et al., 1983
341	0.174	UV, NBKI	2 hr	IE(2 x R) @ 15-min intervals	Increased symptom scores and small significant decreases in FEV_1 (-2.4%), FVC, PEFR, and TLC in both asthmatic and healthy subjects however, 25/34 healthy subjects were allergic and "atypically" reactive to O_3.	34 "healthy" adults 30 asthmatic adults	Linn et al., 1980, 1983

[a] Ranked by lowest observed effect level for O_3 in ambient air.

[b] Measurement method: UV = ultraviolet photometry.

[c] Calibration method: UV = ultraviolet photometry standard; NBKI = neutral buffered potassium iodide.

[d] Minute ventilation reported in L/min or as a multiple of resting ventilation. CE = continuous exercise, IE = intermittent exercise.

actual pollutant levels have not differed enough during the study, or other important variables have not been adequately controlled. The terms "oxidant" and "ozone" and their respective association with health effects are often unclear. Moreover, information about the measurement and calibration methods used is often lacking. Also, as epidemiological methods improve, the incorporation of new key variables into the analyses is desirable, such as the use of individual exposure data (e.g., from the home and workplace). Analyses employing these variables are lacking for most of the community studies evaluated.

Studies of effects associated with acute exposure that are considered to be qualitatively useful for standard-setting purposes include those on irritative symptoms, pulmonary function, and aggravation of existing respiratory disease. Reported effects on the incidence of acute respiratory illness and on physician, emergency room, and hospital visits are not clearly related with acute exposure to ambient O_3 or oxidants and, therefore, are not useful for deriving health effects criteria for standard-setting purposes. Likewise, no convincing association has been demonstrated between daily mortality and daily oxidant concentrations; rather, the effect correlates most closely with elevated temperature.

Studies on the irritative effects of O_3 have been complicated by the presence of other photochemical pollutants and their precursors in the ambient environment and by the lack of adequate control for other pollutants, meteorological variables, and non-environmental factors in the analysis. Although O_3 does not cause the eye irritation normally associated with smog, several studies in the Los Angeles basin have indicated that eye irritation is likely to occur in ambient air when oxidant levels are about 0.10 ppm. Qualitative associations between oxidant levels in the ambient air and symptoms such as eye and throat irritation, chest discomfort, cough, and headache have been reported at >0.10 ppm in both children and young adults (Hammer et al., 1974; Makino and Mizoguchi, 1975). Discomfort caused by irritative symptoms may be responsible for the impairment of athletic performance reported in high school students during cross-country track meets in Los Angeles (Wayne et al., 1967; Herman, 1972) and is consistent with the evidence from field studies (Section 11.2.1) and from controlled human exposure studies (Section 10.4) indicating that exercise performance may be limited by exposure to O_3. Although several additional studies have shown respiratory irritation apparently related to exposure to ambient O_3 or oxidants in community populations, none of these epidemiological studies provide satisfactory quantitative data on acute respiratory illnesses.

Epidemiological studies in children and young adults suggest an association of decreased peak flow and increased airway resistance with acute ambient air exposures to daily maximum 1-hr O_3 concentrations ranging from 20 to 274 $\mu g/m^3$ (0.01 to 0.14 ppm) over the entire study period (Lippmam et al., 1983; Lebowitz et al., 1982a, 1983, 1985; Lebowitz, 1984; Bock et al., 1985; Lioy et al., 1985). None of these studies by themselves can provide satisfactory quantitative data on acute effects of O_3 because of methodological problems along with the confounding influence of other pollutants and environmental conditions in the ambient air. The aggregation of individual studies, however, provides reasonably good evidence for an association between ambient O_3 exposure and acute pulmonary function effects. This association is strengthened by the consistency between the findings from the epidemiological studies and the results from the field studies in exercising adolescents (Avol et al., 1985a,b) which have shown small decreases in forced expiratory volume and flow at 282 $\mu g/m^3$ (0.144 ppm) of O_3 in the ambient air; and with the results from the controlled human exposure studies in exercising children which have shown small decrements in forced expiratory volume at 235 $\mu g/m^3$ (0.12 ppm) of O_3 (Section 10.2.9.2).

In studies of exacerbation of asthma and chronic lung diseases, the major problems have been the lack of information on the possible effects of medications, the absence of records for all days on which symptoms could have occurred, and the possible concurrence of symptomatic attacks resulting from the presence of other environmental conditions in ambient air. For example Whittemore and Korn (1980) and Holguin et al. (1985) found small increases in the probability of asthma attacks associated with previous attacks, decreased temperature, and with incremental increases in oxidant and O_3 concentrations, respectively. Lebowitz et al. (1982a, 1983, 1985) and Lebowitz (1984) showd effects in asthmatics, such as decreased peak expiratory flow and increaed respiratory symptoms, that were related to the interaction of O_3 and temperature. All of these studies have questionable effects from other pollutants, particularly inhalable particles. There have been no consistent finding of symptom aggravation or changes in lung function in patients with chronic lung diseases other than asthma.

Only a few prospective studies have been reported on morbidity, mortality, and chromosomal effects from chronic exposure to O_3 or other photochemical oxidants. The lack of quantitative measures of oxidant exposures seriously limits the usefulness of many population studies of morbidity and mortality for standards-setting purposes. Most of these long-term studies have employed average annual levels of photochemical oxidants or have involved broad ranges of pollutants; others have used a simple high-oxidant/low-oxidant dichotomy. In addition, these population studies are also limited by their inability to control for the effects of other factors that can potentially contribute to the development and progression of respiratory disease over long periods of time. Thus, insufficient information is available in the epidemiological literature on possible exposure-response relationships between ambient O_3 or other photochemical oxidants and the prevalence of chronic lung disease or the rates of chronic disease mortality. None of the epidemiological studies investigating chromosomal changes have found any evidence that ambient O_3 or oxidants affect the peripheral lymphocytes of the exposed population.

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12. EVALUATION OF HEALTH EFFECTS DATA FOR OZONE AND OTHER PHOTOCHEMICAL OXIDANTS

12.1 INTRODUCTION

The preceding chapters (Chapters 9, 10, and 11) have documented a wide array of toxicological responses elicited by in vivo and in vitro exposures to ozone at concentrations of 1 ppm and below and to other photochemical oxidants at various concentrations. The extensive body of data on the health effects of ozone was reported and discussed in particular detail in those chapters. The present chapter examines, in the light of the findings presented in the earlier chapters, specific issues and questions that are important for standard-setting.

Paramount among the issues considered in standard-setting is the identification of one or more groups of people who need to be protected by the regulation; that is, one or more groups of individuals who are at potential risk from exposure to ozone and other photochemical oxidants. The identification of such groups presupposes the identification of one or more effects in man or animals that are in and of themselves adverse, or that are indicators of other effects that are adverse but are not measurable in man because of ethical constraints.

The existing health effects data indicate that ozone can affect structure, function, metabolism, and defense against bacterial infection in the pulmonary system and can produce extrapulmonary effects, as well. These data are drawn from human clinical, field, and epidemiological studies, and from animal toxicological studies. Each of these research approaches, however, has inherent strengths and weaknesses relative to the assessment of risk. No single approach provides an adequate basis for an informed judgment, but together these approaches provide a reasonable estimate of the human health effects of ozone.

In vitro studies on isolated cells and tissues and in vivo studies on laboratory animals permit the measurement of effects under circumstances that are not permissible in clinical research. Such studies can, therefore, be useful for defining concentration-response relationships over a wide range of experimental conditions; for studying responses that can only be examined with invasive procedures; for sorting out and testing hypotheses as a prelude to clinical investigations; and as an aid in the design of epidemiological studies.

This information can be used to examine possible linkages between acute and chronic effects and to correlate biochemical, functional, and structural changes with growth, development, and aging of the lung as the result of exposure to ozone. The chief weakness of laboratory animal studies lies in the difficulties and associated uncertainties of quantitatively extrapolating their results to the healthy human population, and the even greater problems of extrapolating such results to diseased human populations.

Controlled studies on human subjects provide information about sensitive populations, concentration-response relationships, and responses to a limited number of repeated exposures. Subjects can be carefully selected and exposure conditions controlled. Such studies, however, are necessarily restricted to ethically and legally acceptable pollutant concentrations and exposure regimens, as well as to noninvasive techniques for measuring effects. Furthermore, only reversible effects can ethically be studied. The emphasis in studies of human responses to ozone inhalation found in the literature is, therefore, on pulmonary function. The chief weaknesses of controlled human exposure studies are found in the need to (1) restrict studies to short-term exposures; (2) limit the range of pollutant concentrations and type of subjects studied; and (3) use synthetic, simplified atmospheres. Some of these weaknesses are, of course, the very features that constitute the strengths of controlled studies since they permit the determination of concentration-response functions relative to a specific pollutant and specific endpoint.

Field and epidemiological studies are designed to associate various characteristics of human health and function with ambient air concentrations of photochemical oxidants. For the purposes of this document, field studies are defined as laboratory experiments in which the postulated cause of an effect in the population is tested under conditions similar to those found in controlled human studies. Subjects can be carefully selected and exposure conditions closely monitored. Exposure-effect relationships, however, are measured during exposure to existing ambient conditions rather than to artificially generated pollutants. These studies thus form a bridge between the controlled human studies and the more traditional epidemiological studies in which human populations are studied in their normal setting. The effects of communities acutely and chronically exposed to photochemical oxidants are generally assessed by comparing the functional or clinical status of the residents during periods of high or low oxidant concentrations. Occasionally, two or more populations residing in high or low oxidant areas are compared. Investigations within the normal setting are not, or course, without their drawbacks. Accurate and reliable air exposure data are extremely difficult to obtain and often do not include indoor exposure conditions. The information gathered on exposure-effect relationships and results may be confounded by factors such as variations in the time spend out of doors and indoors, variations in activity levels, cigarette smoking, disease status, socioeconomic status, and the coexistence of other pollutants and other environmental conditions. No single epidemiological study can, therefore, provide definitive evidence for effects that can be attributed solely to ozone, but can only indicate whether ambient air levels of ozone and other photochemical oxidants are associated with some measurable outcome of exposure. Although the strength of this evidence may vary from study to study, the aggregation of epidemiological data and their convergence potentially provide stronger evidence for human health effects of ozone.

The responses to ozone and other photochemical oxidants that can be linked most directly to the potential impairment of public health, i.e., without extrapolation, are those changes in pulmonary function that have been observed in controlled human studies of ozone exposure and in certain field studies of human exposure to ambient air containing ozone. Additional, supportive data on related respiratory system effects have been obtained from epidemiological studies of acute exposure to ozone and other photochemical oxidants in ambient air and from toxicological studies in laboratory animals exposed to ozone.

As discussed in the 1978 criteria document for ozone and other photochemical oxidants (U.S. Environmental Protection Agency, 1978), changes in lung function associated with exposure to ozone and other photochemical oxidants are viewed as signalling potential impairment of public health for several reasons. Alterations in lung function potentially interfere with normal activity in the general population and in population groups, depending upon the activity and the population. In the general population, for example, ozone exposure during moderate to heavy exercise can produce significant decrements in lung function (Chapter 10). In certain individuals in the general population, not yet characterized medically except by their response to ozone, significant decrements, larger than those seen in the rest of the general population, are elicited by exposure to ozone during either continuous or intermittent exercise. In individuals who have respiratory diseases such as asthma or chronic obstructive lung disease, even small decrements in lung function could potentially interfere with normal activity and might be of clinical significance. Symptoms usually accompany the observed decrements in lung function and impairments in other respiratory indicators, especially during exercise.

> Thus, at least when associated with ozone exposure, changes in lu[illegible] function often represent a level of discomfort that, even amon[illegible] healthy people, may restrict normal activity or impair the perf[illegible] mance of tasks.
>
> (U.S. Environmental Protection Agency, 19[illegible]

To evaluate the health effects documented and described in t[illegible] [illegible]eding chapters, relevant effects and the identification of potential[illegible] [illegible]isk individuals and groups are discussed at length in this chapter. I[illegible] [illegible]dition, inherent biological characteristics or personal habits and activities that may attenuate or potentiate typical responses to ozone and other oxidants are discussed. The environmental factors that determine potential or real exposures of populations or groups are presented, as well, including known ambient air concentrations of ozone, of other related photochemical oxidants, and of these combined oxidants.

The issues discussed in subsequent sections are enumerated below:

1. Concentrations and patterns of ozone and other photochemical oxidants, including indoor-outdoor gradients, relevant for exposure assessment.
2. Symptomatic effects of ozone and other photochemical oxidants.
3. Effects of ozone on pulmonary function in the general population, at rest and with exercise and other stresses.
4. Influence on the effects of ozone of age, sex, smoking status, nutritional status, and red-blood-cell enzyme deficiencies.
5. Effects of repeated exposure to ozone.
6. Effects of ozone on lung structure and the relationship between acute and chronic effects from ozone exposure.
7. Effects of ozone related to resistance to infections, i.e., host defense mechanisms.
8. Effects of ozone on extrapulmonary tissues, organs, and systems.
9. Effects of ozone in individuals with preexisting disease.

10. Extrapolation to human populations of ozone/oxidant effects observed in animals.
11. Effects of other photochemical oxidants and the interactions of ozone and other pollutants.
12. Identification of potentially-at-risk groups.
13. Demographic information on potentially at-risk groups.

12.2 EXPOSURE ASPECTS

Certain information about the occurrence of ozone and other photochemical oxidants is important for assessing both the potential and the actual exposures of individuals and of populations. In this section, air monitoring data are summarized as background information for relating the concentrations at which effects have been observed in health studies to the occurrence of ozone and other oxidants in ambient air; and as background for estimating exposures.

12.2.1 Potential Exposures to Ozone

Ozone concentrations exhibit fairly strong diurnal and seasonal cycles. In most urban areas, single or multiple peaks of ozone occur during daylight hours, usually during midday (e.g., about noon until 3:00 or 4:00 p.m.). The formation of ozone and other photochemical oxidants from precursor emissions is limited to daylight hours since the chemical reactions in the atmosphere are driven by sunlight. Because of the intensity of sunlight necessary and the other meteorological and climatic conditions required, the highest concentrations of ozone and other photochemical oxidants usually occur during the second and third quarters of the year, i.e., April through September. The months of highest ozone concentrations depend, however, upon local or regional weather patterns to a considerable degree, so that the temporal patterns of ozone concentrations are location-dependent. In California, for example, October is usually a month of higher ozone concentrations than April, and therefore the 6-month period of highest average ozone concentrations appears typically to be May through October in many California cities and conurbations.

Although most peak ozone concentrations occur during daylight hours in nonurban areas, peak concentrations in the early evening and at night are not uncommon. The occurrence of nighttime peaks appears to be the result of combined induction time and transport time for urban plumes, coupled with the lack of nitric oxide (NO) sources to provide NO for chemical scavenging of ozone in the evening and early morning hours. Average ozone concentrations are generally lower in nonurban than in urban areas, but peak concentrations higher than those found in urban and suburban areas can sometimes occur.

In urban areas, early morning ozone concentrations (around 2:00 or 3:00 a.m. until about 6:00 a.m.) are near zero (<0.02 ppm), largely because of scavenging by NO. In nonurban areas, early morning ozone concentrations are higher and are near background levels (e.g., about 0.025 to 0.045 ppm), since surface scavenging rather than chemical scavenging by NO is the principal removal mechanism in nonurban areas.

Quantitative data on ozone concentrations are briefly summarized here. Figure 12-1 shows the frequency distribution of the three highest 1-hour ozone concentrations in each year aggregated for 3 years (1979 through 1981) (U.S. Environmental Protection Agency, 1980, 1981, 1982). These three curves are based on data obtained from predominantly urban monitoring stations. The frequency distribution of the highest 1-hour concentrations measured at eight rural or remote sites (Evans, 1985) is presented separately in Figure 12-1. These 1-hour concentrations, recorded at sites of the National Air Pollution Background Network (NAPBN) located in national forests across the country, have been aggregated for the same 3-year period, 1979 through 1981. The present primary and secondary national ambient air quality standards for ozone are expressed as a concentration not to be exceeded on more than one day per year. Thus, the second-highest value among daily maximum 1-hour ozone concentrations, rather than the highest, is regarded as a concentration indicative of the degree of protection of public health and welfare. As demonstrated by Figure 12-1, 50 percent of these values reported at the urban monitoring stations, aggregated for 3 years, were $\simeq$ 0.12 ppm; 25 percent were $\simeq$ 0.15 ppm; and 10 percent were $\simeq$ 0.20 ppm. The frequency distribution of the daily maximum (i.e., the highest) 1-hour concentrations measured at NAPBN sites shows that 50 percent of the concentrations were $\leq$ 0.09 ppm; 25 percent were $\leq$ 0.08 ppm; and 10 percent were $\leq$ 0.07 ppm.

As data in Chapter 10 and in Section 12.3.4 show, human controlled-exposure studies have demonstrated that attenuation of responses to ozone during repeated, consecutive-day exposures of at least 3 to 4 days occurs in many, though not all, of the individuals studied. Thus, the potential for repeated, consecutive-day exposures of that duration to ambient air concentrations of

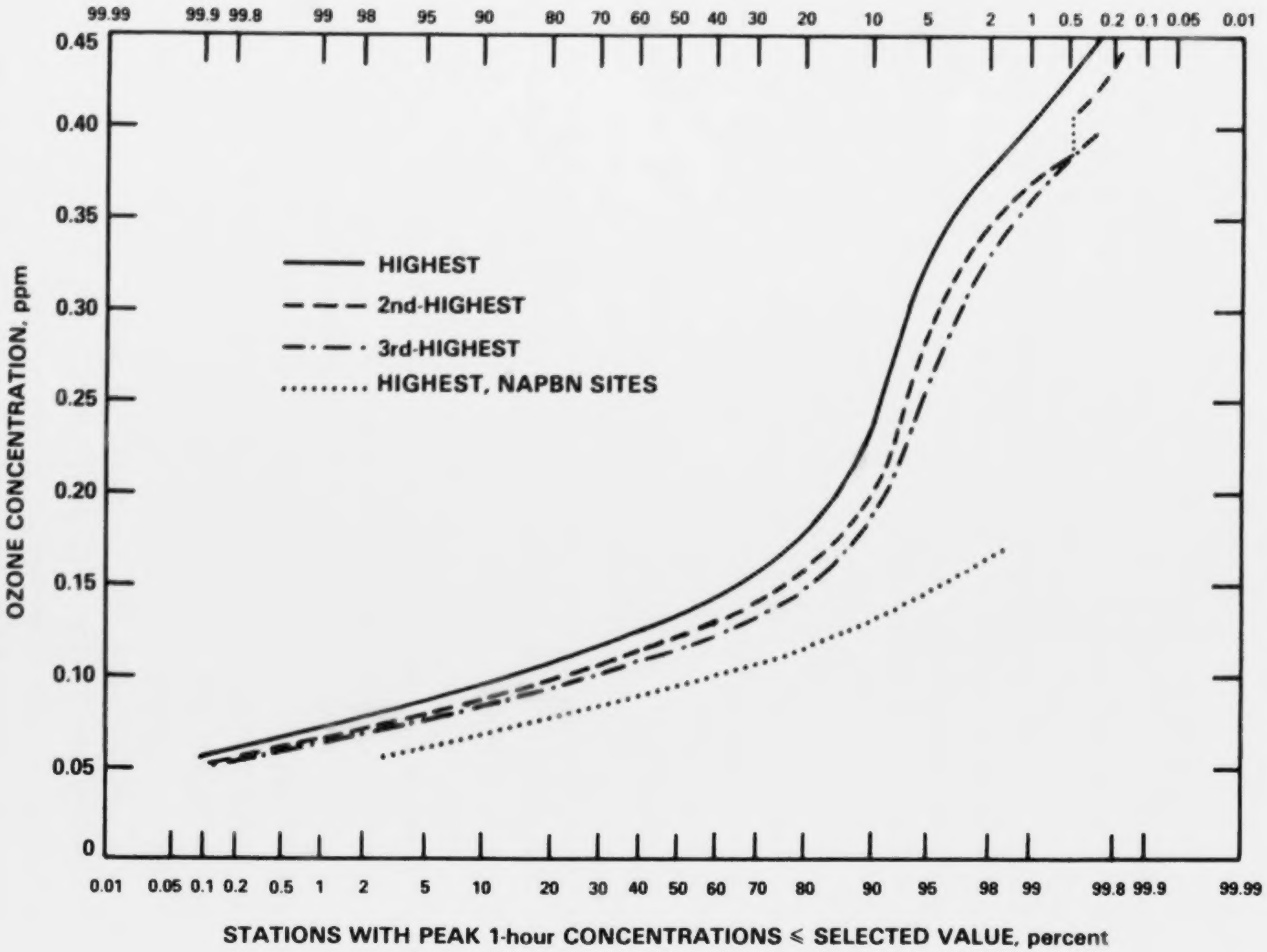

Figure 12-1. Distributions of the three highest 1-hour ozone concentrations at valid sites (906 station-years) aggregated for 3 years (1979, 1980, and 1981) and the highest ozone concentrations at NAPBN sites aggregateed for those years (24 station-years).

Source: U.S. Environmental Protection Agency (1980, 1981, 1982).

ozone is of interest. Data records from four cities were examined in Chapter 5 for exposures to four different 1-hour concentrations to determine their recurrence on 2 or more consecutive days in a 3-year period (see Tables 5-6 through 5-9). Those data are summarized for three cities in Table 12-1. The data given in Table 12-1 are descriptive statistics based on aerometric data from the respective localities for 1979, 1980, and 1981, and cannot be used to predict the number of recurrences of high 1-hour concentrations of ozone for any other period or locality. The 1-hour ozone concentration at the Pasadena, CA, site reached a 1-hour concentration $\geq$ 0.18 ppm for 4 consecutive days six times and for 8 or more consecutive days seven times in the 3-year period examined. A 1-hour concentration $\geq$ 0.24 ppm was reached on 4 consecutive days two times and 8 or more consecutive days one time in the 3 years. Data for sites in Dallas, TX, and Washington, DC, show no consecutive-day recurrences of high 1-hour concentrations such as those sustained in Pasadena. Data presented in Chapter 5 for a Pomona, CA, site, also in the South Coast Air Basin, show a pattern similar to that in Pasadena of consecutive-day recurrences of high 1-hour ozone concentrations.

Potential exposures of nonurban populations, while not easily ascertained in the absence of a suitable aerometric data base, can be estimated from measurements made at selected sites known to represent agricultural areas and at sites of special-purpose monitoring networks. Data from the eight NAPBN national forest (NF) monitoring stations show that arithmetic mean 1-hour ozone concentrations at these sites, for the second and third quarters of the year, ranged from a 5-year average of 25.8 ppb at Kisatchie NF, LA (1977-1980, 1982) to a 4-year average of 49.4 ppb at Apache NF, AZ (1980-1983) (Evans, 1985). (Data are weighted for the number of 1-hour concentrations measured.) Data from Sulfate Regional Experiment (SURE) sites showed mean concentrations of ozone for August through December 1977 at four "rural" sites of 0.021, 0.029, 0.026, and 0.035 ppm at Montague, MA, Duncan Falls, OH, Giles County, TN, and Lewisburg, WV, respectively. At five "suburban" SURE sites (Scranton, PA; Indian River, DE; Rockport, IN; Ft. Wayne, IN; and Research Triangle Park, NC), mean concentrations for the study period were 0.023, 0.030, 0.025, 0.020, and 0.025 ppm, respectively. Maximum 1-hour ozone concentrations for the nine stations ranged from 0.077 ppm at Scranton, PA, to 0.153 ppm at Montague, MA (Martinez and Singh, 1979).

TABLE 12-1. NUMBER OF TIMES THE DAILY MAXIMUM 1-hr OZONE CONCENTRATION WAS ≥ 0.06, ≥ 0.12, ≥ 0.18, and ≥ 0.24 ppm FOR SPECIFIED CONSECUTIVE DAYS IN PASADENA, DALLAS, AND WASHINGTON, APRIL THROUGH SEPTEMBER, 1979 THROUGH 1981

City and no. of consecutive days	No. of occurrences of daily max. 1-hr O_3 concns of: ≥0.06 ppm	≥ 0.12 ppm	≥ 0.18 ppm	≥ 0.24 ppm
Pasadena				
2	5[a]	10	9	13
3	0	8	10	5
4	2	4	6	2
5	2	7	3	2
6	0	2	4	0
7	2	0	1	0
≥8	10	14	7	1
Dallas				
2	10	4	0	0
3	6	2	0	0
4	5	0	0	0
5	8	1	0	0
6	3	0	0	0
7	5	0	0	0
≥8	11	0	0	0
Washington				
2	10	1	0	0
3	6	0	0	0
4	2	0	0	0
5	2	0	0	0
6	0	0	0	0
7	2	0	0	0
≥8	5	0	0	0

[a] Note: Data are not cumulative by row or by column. This is because an episode in which, for example, a 1-hour concentration of 0.18 ppm is exceeded on each of 2 consecutive days is almost always part of a longer episode in which a lower 1-hour concentration (e.g., 0.12 or 0.06 ppm) has been exceeded on each day of an even longer consecutive-day period. Thus, the occurrences of a 2-day episode at a higher concentration, for example, are a subset of the occurrences of an *n*-day episode (e.g., ≥ 3 days) tabulated under one or more lower concentrations.

Source: SAROAD (1985a,b,c).

Concentrations of ozone indoors, since most people spend most of their time indoors, are of value in estimating total exposures. The estimation of total exposures, in turn, is of value for optimal interpretation and use of epidemiological studies. Data on concentrations of ozone indoors are few. It is known, however, that ozone decays fairly rapidly indoors through reactions with surfaces of such materials as wall board, carpeting, and draperies (Chapter 5). Ozone concentrations indoors depend also on those factors that affect both reactive and nonreactive pollutants: concentrations outdoors, temperature, humidity, air exchange rates, presence or absence of air conditioning, and mode of air conditioning (e.g., 100 percent fresh-air intake versus recirculation of air). Estimates in the literature on indoor-outdoor ratios (I/O, expressed as percentage) of ozone concentrations range from just over 0 percent to 100 percent for residences (Stock et al., 1983), and from 29 percent (Moschandreas et al., 1978) to 80 ± 10 percent (Sabersky et al., 1973) for office buildings. Variations in estimated I/O for buildings are attributable to the diversity of structures monitored, their locations, and their heating, ventilating, and air-conditioning systems. Measurements made inside automobiles show inside ozone concentrations ranging from about 30 percent (Peterson and Sabersky, 1975) to about 56 percent (Contant et al., 1985) of outside concentrations. Again, outside concentrations and mode of air conditioning or ventilation are among the factors determining the inside concentrations. It should be noted that outside concentrations of ozone on well-traveled roadways are lower than other outdoor concentrations because nitric oxide emissions from automobiles scavenge ozone.

Along with small-scale spatial variations in ozone concentrations, such as indoor-outdoor gradients, large-scale variations exist, such as those that occur with latitude and altitude. Latitudinal variations have little effect on potential exposures within the contiguous United States, since the contiguous states all fall within latitudes where photochemical oxidant formation is favored (Logan et al., 1981; U.S. Environmental Protection Agency, 1978). The increases in concentrations of background ozone with increase with altitude (Viezee et al., 1979; Seiler and Fishman, 1981) are significant only in the free troposphere. When ozone is carried in layers aloft in long-distance transport (i.e., mesoscale and synoptic-scale transport), it is conserved overnight because of the occurrence of temperature inversions (nocturnal inversions) that prevent downward vertical mixing and thus prevent scavenging at the surface by the nitric oxide present in ground-level emissions. Where nocturnal inversion layers contact mountainsides, ozone concentrations will be greater at night at higher elevations than at lower. Daytime concentrations may vary slightly but not appreciably with elevation. Daytime peak concentrations may occur later in the day at higher elevations because of transport time from urban sources, most of which are at lower elevations. There appear to be fewer implications for human populations than for mountain forests and other vegetation, however, since high elevations are usually sparsely populated and since the higher concentrations observed at higher elevations occur overnight. The altitudinal gradients in the free troposphere could be of possible consequence for certain high-altitude flights, as reported in the field studies documented in Chapter 11, except that the air filtration and ventilation systems commonly employed on airplanes reduce the on-board concentrations.

It should be pointed out that the mass of ozone per unit volume decreases with elevation (altitude), for given concentrations expressed as volume/volume ratios. In addition, data presented in Chapter 5 for Denver, CO, for example, show that ozone concentrations are lower there than at many lower-elevation metropolitan areas of comparable size.

Even though ozone is considered to be a regional pollutant, intermediate-scale spatial variations in concentrations occur that are of potential consequence for designing and interpreting epidemiological studies. For example, data from a study of ozone formation and transport in the northeast corridor (Smith, 1981) showed that in New York City an appreciable gradient existed, at least for the study period (summer, 1980), between ozone concentrations in Brooklyn and those in the Bronx. The maximum 1-hour ozone concentration measured at the Brooklyn monitoring site was 0.174 ppm, while that measured at the Bronx monitoring site was 0.080 ppm.

12.2.2 Potential Exposures to Other Photochemical Oxidants

12.2.2.1 Concentrations. Concentrations in ambient air of four photochemical oxidants other than ozone have been presented in Chapter 5. Those data are drawn upon here to examine the concentrations of these pollutants that might be encountered in the United States, including "worst-case" situations, in order to determine both the minimum and maximum additive concentrations of these pollutants with ozone that could occur in ambient air. The four photochemical oxidants for which concentration data were given in Chapter 5 are peroxyacetyl nitrate (PAN), peroxypropionyl nitrate (PPN), hydrogen peroxide (H_2O_2), and formic acid (HCOOH).

Although they co-occur to varying degrees with ozone, aldehydes are not photochemical oxidants. Since they are not oxidants and are not measured by methods that measure oxidants, their role relative to public health and welfare is not reported in this document. The reader is referred to a recent comprehensive review by Altshuller (1983) for a treatment of the relationships in ambient air between ozone and aldehyde concentrations.

Few health effects data or aerometric data on formic acid exist. Those ambient air concentrations that are given in the literature, however, indicate that formic acid occurs at trace concentrations, i.e., $\leq$0.015 ppm, even in high-oxidant areas such as the South Coast Air Basin of California (Tuazon et al., 1981). No data are available for other urban areas or for nonurban areas. Given the known atmospheric chemistry of formic acid, concentrations in the South Coast Air Basin are expected to be higher than in other urban areas of the country (Chapter 3).

The measurement methods (IR and GC-ECD) for PAN and PPN are specific and highly sensitive, and have been in use in air pollution research for nearly two decades. Thus, the more recent literature on the concentrations of PAN and PPN confirm and extend, but do not contradict, earlier findings reported in the two previous criteria documents for ozone and other photochemical oxidants (U.S. Department of Health, Education, and Welfare, 1970; U.S. Environmental Protection Agency, 1978).

Concentrations of PAN are reported in the literature from 1960 through the present. The highest concentrations reported over this extended period were those found in the 1960s in the Los Angeles area: 70 ppb (1960), 214 ppb (1965), and 68 ppb (1968) (Renzetti and Bryan, 1961; Mayrsohn and Brooks, 1965; Lonneman et al., 1976, respectively).

The highest concentrations of PAN measured and reported in the past 5 years were 42 ppb at Riverside, CA, in 1980 (Temple and Taylor, 1983), and 47 ppb at Claremont, CA, also in 1980 (Grosjean, 1983). These are clearly the maximum concentrations of PAN reported for California and for the entire country in this period. Other recently measured PAN concentrations in the Los Angeles Basin were in the range of 10 to 20 ppb. Average concentrations of PAN in the Los Angeles Basin in the past 5 years ranged from 4 to 13 ppb (Tuazon et al., 1981; Grosjean, 1983). The only published report covering PAN concentrations outside California in the past 5 years is that of Lewis et al. (1983) for New Brunswick, NJ. The average PAN concentration there was 0.5 ppb and the maximum was 11 ppb during a study done from September 1978 through May 1980. Studies outside California from the early 1970s through 1978 showed average PAN concentrations ranging from 0.4 ppb in Houston, TX, in 1976 (Westberg et al., 1978) to 6.3 ppb in St. Louis, MO, in 1973 (Lonneman et al., 1976). Maximum PAN concentrations outside California for the same period ranged from 10 ppb in Dayton, OH, in 1974 (Spicer et al., 1976) to 25 ppb in St. Louis (Lonneman et al., 1976).

The highest PPN concentration reported in studies from 1963 through the present was 6 ppb in Riverside, CA, in the early 1960s (Darley et al., 1963). The next highest reported PPN concentration was 5 ppb at St. Louis, MO, in 1973 (Lonneman et al., 1976). Among more recent data, maximum PPN concentrations at respective sites ranged from 0.07 ppb in Pittsburgh, PA (Singh et al., 1982) to 3.1 ppb at Staten Island, NY, in 1981 (Singh et al., 1982). California concentrations fell within this range. Average PPN concentrations at the respective sites for the more recent data ranged from 0.05 ppb at Denver and Pittsburgh to 0.7 ppb at Los Angeles in 1979 (Singh et al., 1981).

Altshuller (1983) has succinctly summarized the nonurban concentrations of PAN and PPN by pointing out that they overlap the lower end of the range of urban concentrations at sites outside California. At remote locations, PAN and PPN concentrations are lower than even the lowest of the urban concentrations (by a factor of three to four).

Concentrations of H_2O_2 reported in the published literature must be regarded as inaccurate, since all wet-chemical methods used to date are now thought to be subject to positive interference from ozone. Evidence that reported H_2O_2 concentrations have been in error is provided not only by recent investigations of wet-chemical methods, but by the fact that FTIR measurements of ambient air have not demonstrated the presence of H_2O_2 even in the high-oxidant atmosphere of the Los Angeles area. The limit of detection for a 1-km-pathlength FTIR system, which can measure H_2O_2 with specificity, is around 0.04 ppm (Chapter 4). In urban areas, hydrogen peroxide (H_2O_2) concentrations have been reported to range from $\leq$ 0.5 ppb in Boulder, CO (Heikes et al., 1982) to $\leq$ 180 ppb in Riverside, CA (Bufalini et al., 1972). In nonurban areas, reported concentrations ranged from 0.2 ppb near Boulder, CO, in 1978 (Kelly et al., 1979) to $\leq$ 7 ppb 54 km southeast of Tucson, AZ (Farmer and Dawson, 1982). These nonurban data were obtained by the luminol chemiluminescence technique (see Chapter 4). The urban data were obtained by a variety of methods, including the luminol chemiluminescence, the titanium (IV) sulfate 8-quinolinol, and other wet chemical methods (see Chapter 4). Thus, these reported concentrations have all been measured by methods in which ozone is a positive interference.

12.2.2.2 Patterns. The patterns of formic acid (HCOOH), PAN, PPN, and H_2O_2 can be summarized fairly succinctly. They bear qualitative but not quantitative resemblance to the patterns already summarized for ozone concentrations. Qualitatively, diurnal patterns are similar, with peak concentrations of each of these occurring in close proximity to the time of the ozone peak. The correspondence in time of day is not exact, but is close. As the work of Tuazon et al. (1981) at Claremont, CA, demonstrates (see Chapter 5) ozone concentrations return to baseline levels faster than the concentrations of PAN, HCOOH, or H_2O_2 (PPN was not measured).

Seasonally, winter concentrations (first and fourth quarters) of PAN are lower than summer concentrations (second and third quarters). The winter concentrations of PAN are proportionally higher relative to ozone in winter than in summer. Data are not available on the seasonal patterns of the other non-ozone oxidants.

Indoor-outdoor data on PAN are limited to one report (Thompson et al., 1973), which confirms the pattern to be expected from the known chemistry of PAN; that is, it persists longer indoors than ozone. Data are lacking for indoor concentrations of the other non-ozone oxidants.

12.2.3 Potential Combined Exposures and Relationship of Ozone and Other Photochemical Oxidants

Data on concentrations of PAN, PPN, and H_2O_2 indicate that in "worst-case" situations these non-ozone oxidants together could add as much as about 0.15 ppm of oxidant to the ozone burden in ambient air. The highest of the "second-highest" ozone concentration measured in the United States in 1983 was 0.37 ppm, in the Los Angeles area. (For the definition of the "second-highest" 1-hour value see Chapter 5). In the presence of that concentration of ozone, the addition of "worst-case" concentrations of non-ozone oxidants (0.15 ppm total) would bring the total oxidant concentration to around 0.52 ppm, provided peak concentrations of ozone and non-ozone oxidants were reached at the same time. It should be noted that such "worst-case" concentrations are not viewed as typical. Data from recent years for the Los Angeles Basin indicate that average concentrations of PAN and PPN together would add 0.014 ppm (14 ppb) to the average oxidant burden there (4 to 13 ppb average PAN: Tuazon et al., 1981; Grosjean, 1983, respectively; and 0.7 ppb PPN: Singh et al., 1981).

The significance for public health of the imposition of an additional oxidant burden from non-ozone oxidants rests not only on average or "worst-case" concentrations, however, but on the answers to at least several other questions, e.g.:

1. Do PAN, PPN, or H_2O_2, singly or in combination, elicit adverse or potentially adverse responses in human populations?
2. Do any or all of these non-ozone oxidants act additively or synergistically in combination with ozone to elicit adverse or potentially adverse responses in human populations? Do any or all act antagonistically with ozone?
3. What is the relationship between the occurrence of ozone and these non-ozone oxidants? Can ozone serve as a surrogate for these other oxidants?

The first two questions are addressed by health effects data presented in Chapters 9 through 11 and in Section 12.6 of the present chapter. The third question has been addressed in detail by Altshuller (1983). His conclusion is that "the ambient air measurements indicate that O_3 may serve directionally, but cannot be expected to serve quantitatively as a surrogate for the other products" (Altshuller, 1983). It must be emphasized here that Altshuller examined the issue of whether O_3 could serve as an abatement surrogate for all photochemical products, including those not relevant to effects data examined in this document. For example, the products he reviewed relative to ozone included aldehydes, aerosols, and nitric acid. Nevertheless, his conclusions appear to apply to the subset of photochemical products of concern here: PAN, PPN, and H_2O_2.

The most straightforward evidence of the lack of a quantitative, monotonic relationship between ozone and the other photochemical oxidants is the range of PAN-to-O_3 ratios and, indirectly, of PAN-to-PPN ratios presented in the review by Altshuller (1983) and summarized in Table 12-2 and in Chapter 5.

TABLE 12-2. RELATIONSHIP OF OZONE AND PEROXYACETYL NITRATE AT URBAN AND SUBURBAN SITES IN THE UNITED STATES IN REPORTS PUBLISHED 1978 OR LATER

Site/year of study	PAN/O_3, %		Reference
	Avg.	At O_3 peak	
West Los Angeles, CA, 1978	9	6	Hanst et al. (1982)
Claremont, CA, 1978	7	6	Tuazon et al. (1981a, 1981b)
Claremont, CA, 1979	4	4	Tuazon et al. (1981a)
Riverside, CA, 1975-1976	9	5	Pitts and Grosjean (1979)
Riverside, CA, 1976	5	4	Tuazon et al. (1978)
Riverside, CA, 1977	4	4	Tuazon et al. (1980)
Riverside, CA, 1977	4	NA[a]	Singh et al. (1979)
Houston, TX, 1976	3	3	Westberg et al. (1978)
New Brunswick, NJ, 1978-1980	4	2	Brennan (1980)

[a] Not available.

Source: Derived from Altshuller (1983). For primary references, see Chapter 5.

Certain other information presented in Chapter 5 bears out the lack of a strictly quantitative relationship between ozone and PAN and its homologues. Not only are ozone-PAN relationships not consistent between different urban areas (e.g., Singh et al., 1982), but they are not consistent in urban versus nonurban areas (e.g., Lonneman et al., 1976), in summer versus winter (e.g., Temple and Taylor, 1983), in indoor versus outdoor environments (Thompson et al., 1973), or even, as the ratio data show, in location, timing, or magnitude of diurnal peak concentrations within the same city (e.g., Jorgen et al., 1978). In addition, Tuazon et al. (1981) demonstrated that PAN persists in ambient air longer than ozone, its persistence paralleling that of HNO_3, at least in some localities. Reactivity data presented in the 1978 criteria document for ozone and other photochemical oxidants indicate that all precursors that give rise to PAN also give rise to ozone. Not all are equally reactive toward both products, however, and therefore some precursors preferentially give rise, on the basis of units of product per unit of reactant, to more of one product than the other (U.S. Environmental Protection Agency, 1978).

It must be emphasized that information presented in Chapter 4 clearly shows that no one method can quantitatively and reliably measure all four oxidants of potential concern (ozone, PAN, PPN, and hydrogen peroxide), either one at a time or in ambient air mixtures. This point was not clearly presented in the 1978 criteria document but is given substantial discussion in Chapter 4 of this document.

12.3 HEALTH EFFECTS IN THE GENERAL HUMAN POPULATION

12.3.1 Clinical Symptoms

A close association has been observed between the occurrence of respiratory symptoms and changes in pulmonary function in adults acutely exposed in environmental chambers to O_3 (Chapter 10) or to ambient air containing O_3 as the predominant pollutant (Chapter 11). This association holds for both the time-course and magnitude of effects. Insofar as cough and chest pain or irritation may interfere with the maximal inspiratory or expiratory efforts (see Section 12.3.5), such associations between symptoms and function might be expected. In a comparison of adults exposed to both oxidant-polluted ambient air and purified air containing only O_3 (Avol et al., 1984, 1985c), no evidence was found to suggest that any pollutant other than O_3 contributed to the symptom increases associated with decrements in lung function. Studies on children and adolescents exposed to O_3 or ambient air containing O_3 under similar conditions have found no significant increases in symptoms despite significant changes in pulmonary function (Avol et al., 1985a,b; McDonnell et al., 1985b,c).

Epidemiological studies have been conducted to compare the incidence of acute, irritative symptoms associated with exposure of communities to varying concentrations of photochemical oxidants, but to date no studies have been designed specifically to test the comparative frequency or magnitude of response of symptoms versus functional changes. In addition, epidemiological studies have been complicated by (1) the presence of other pollutants, including photochemical pollutants and their precursors, in the ambient environment and (2) the lack of adequate control for other pollutants, meteorological variables, and non-environmental factors in the analysis. The symptoms most likely to occur within the polluted community are difficult to associate with a specific pollutant and are, therefore, of limited use for quantifying exposure-response relationships.

The symptoms found in association with controlled exposure to O_3 and with exposure to photochemical air pollution are similar but not identical. Eye irritation, one of the commonest complaints associated with photochemical pollution, is not characteristic of controlled exposures to O_3 alone or to ambient air containing predominantly O_3, even at concentrations of the gas several times higher than any likely to be encountered in ambient air. Other components of photochemical air pollution, such as aldehydes and PAN, are held to be chiefly responsible for eye irritation (National Air Pollution Control Administration, 1970; Altshuller, 1977; National Research Council, 1977; U.S. Environmental Protection Agency, 1978; Okawada et al., 1979).

There is limited qualitative evidence to suggest that at low concentrations of O_3, symptoms other than eye irritation are more likely to occur in populations exposed to ambient air pollution than in subjects exposed in chamber studies, especially if O_3 is the sole pollutant administered in the chamber studies. The symptoms may be indicative of either upper or lower respiratory tract irritation. For example, in two epidemiological studies, qualitative associations between oxidant levels and symptoms such as throat irritation, chest discomfort, cough, and headache have been reported at > 0.10 ppm in both children and young adults (Hammer et al., 1974; Makino and Mizoguchi, 1975). While some individual subjects have experienced cough, shortness of breath, and pain upon deep inspiration at O_3 concentrations as low as 0.12 ppm during controlled exposure with exercise (McDonnell et al., 1983), the group mean symptom response was significant only for cough. It is not clear, however, if the symptoms reported in the epidemiological studies cited above could have been induced by other pollutants in the ambient air. Above 0.12 ppm O_3, a variety of both respiratory and non-respiratory symptoms have been reported in controlled exposures. They include throat dryness, difficulty or pain when inspiring deeply, chest tightness, substernal soreness or pain, cough, wheeze, lassitude, malaise, headache, and nausea (DeLucia and Adams, 1977; Kagawa and Tsuru, 1979b; McDonnell et al., 1983; Adams and Schelegle, 1983; Avol et al., 1984, 1985c; Gibbons and Adams, 1984; Folinsbee et al., 1984; Kulle et al., 1985). Most "symptom scores" have been positive at concentrations of 0.2 ppm O_3 and above. Symptoms tend to remit within hours after exposure is ended. Relatively few subjects have reported persistence of symptoms beyond 24 hours.

Many variables could possibly explain differences in symptomatic effects reported in epidemiological and controlled human studies. They include different subject populations, pollutant mixtures, and exposure patterns utilized in each study, factors affecting the perception of symptoms in one type of study compared to the other, or differences in the methods used to assess symptoms. Alternatively, the presence of reactive chemical species other than O_3 in polluted ambient air might be chiefly responsible for the symptoms observed in epidemiological studies or might interact synergistically with O_3 to initiate the symptoms, although recently published data show no excess response to oxidant-polluted air containing predominantly O_3 and particles (Avol et al., 1984, 1985c).

Symptoms have commonly been assessed by the use of recording sheets combined with reliance on the subject's recall, usually right after exposure but sometimes several hours or days after exposure (e.g., community studies). While it is difficult to score the intensity of symptoms with confidence, the types of symptoms obtained immediately after exposure have been noteworthy for their general consistency across studies. Moreover, as noted earlier, a good association has been observed between changes in symptoms and objective functional tests at O_3 concentrations > 0.15 ppm. Symptoms are therefore considered to be useful adjuncts for assessing the effects of O_3 and photochemical pollution, particularly if combined with objective measurements of pulmonary function.

12.3.2 Pulmonary Function at Rest and with Exercise and Other Stresses

12.3.2.1 At-Rest Exposures. The great majority of short-term ozone exposure studies on resting subjects were published almost a decade ago and were reviewed extensively in the previous ozone-oxidants criteria document (U.S. Environmental Protection Agency, 1978). Briefly, resting subjects inhaling ozone at concentrations up to 0.75 ppm for 2 hr showed no decrements or only very small (< 10 percent) decrements in FVC (Silverman et al., 1976; Folinsbee et al., 1975; Bates et al., 1972), VC (Silverman et al., 1976; Folinsbee et al., 1975), FEV_1, and FRC (Silverman et al., 1976). Other flow-derived variables, such as the maximal expiratory flow at 50 percent VC (FEF 50%) and the maximal expiratory flow at 25 percent VC (FEF25%), were affected to a greater degree, showing decreases of up to 30 percent from control in certain individuals at 0.75 ppm O_3 (Bates et al., 1972; Silverman et al., 1976). Small increases in airway resistance (R_{aw} < 17 percent) were reported at concentrations greater than 0.5 ppm (Bates et al., 1972; Golden et al., 1978). Specific tests of lung mechanical properties generally exhibited a lack of significant effects. Static compliance (C_{st}) remained virtually unchanged, whereas dynamic compliance (C_{dyn}) and the maximum static elastic recoil pressure of the lung (P_{tp} max) showed some borderline effects at 0.75 ppm O_3 (Bates et al., 1972). Ventilatory (V_T, f_B, $\dot{V}_E$) and metabolic ($\dot{V}O_2$, $\dot{V}_E/O_2$) responses to ozone, even at 0.75 ppm level, were not significantly altered (Folinsbee et al., 1975). The only non-spirometric test reported to be significantly affected by ozone inhalation was a bronchial response. Post-ozone (0.6 ppm for 2 hr) challenge with histamine showed significant enhancement of airway responsiveness in every subject tested. Premedication with atropine blocked only transiently the ozone-induced hyperreactivity of airways (SR_{aw}) to histamine (Golden et al., 1978). Breathing 0.6 to 0.8 ppm O_3 for 2 hr markedly reduced diffusion capacity (D_{Lco}) across the alveolar-capillary membrane (Young et al., 1964); however, the mean fractional CO uptake, also an index of diffusion, decreased only marginally under similar exposure conditions (Bates et al., 1972). The slope of phase III of the single-breath nitrogen closing volume curves, which increases as the inhomogeneity in the distribution of ventilation increases, was not significantly altered by O_3 inhalation (Silverman et al., 1976).

More recent at-rest ozone exposure studies basically confirmed previously reported findings. Decrements in forced expiratory volume and flows have been found from exposures to concentrations at and above 0.5 ppm (Folinsbee et al., 1978; Horvath et al., 1979). Airway resistance was not significantly affected at these O_3 concentrations, and static lung volume changes (increase in RV and decrease in TLC) were only suggestive (Shephard et al., 1983). Metabolic and cardiopulmonary effects were also minimal (Horvath et al., 1979). At concentrations below 0.5 ppm ozone, the effects assessed by commonly used pulmonary function tests were small and inconsistent (Folinsbee et al., 1978; Horvath et al., 1979). Reports, however, of ozone-induced symptoms and functional effects in some subjects, well exceeding the group mean response, indicate that even under resting exposure conditions some subjects are more responsive to ozone (König et al, 1980; Lategola et al., 1980a,b; Golden et al., 1978).

12.3.2.2 Exposures with Exercise. Minute ventilation ($\dot{V}_E$) is considered to be one of the principal modulators of the magnitude of response to O_3. The most convenient physiological procedure for increasing $\dot{V}_E$ is to exercise exposed individuals either on a treadmill or bicycle ergometer. Consequent increases in frequency and depth of breathing will increase the overall volume of inhaled pollutant. Moreover, such a ventilatory pattern also promotes penetration of ozone into peripheral lung regions. Thus, a larger amount of ozone will reach tissues most sensitive to injury. These processes are further enhanced at higher workloads ($\dot{V}_E$ > 35 L/min), since the mode of breathing will change from nasal to oronasal or oral only (Niinimaa et al., 1980). As the ventilation increases, an increasingly greater portion of the total minute volume is inhaled orally, bypassing the scrubbing capacity of the nose and nasopharynx (Niinimaa et al., 1981) and further augmenting the ozone dose to the lower airways and parenchyma.

Even in well-controlled experiments on an apparently homogeneous group of subjects, physiological responses to the same work and pollutant loads can vary widely among individuals (Chapter 10). Under strenuous exposure conditions ($\dot{V}_E$ = 45-51 L/min at 0.4 ppm) the least responsive subjects showed FEV_1 decrements of less than 10 percent, while the most responsive yet apparently healthy individuals had severely impaired lung function (FEV_1 = 40 percent of control); the average decrement was 26 percent (Haak et al., 1984; Silverman et al., 1976). Some factors, such as the mode of ventilation (oral versus nasal) and the pattern of breathing (shallow rapid versus slow deep) contribute to but cannot account totally for the commonly observed heterogeneous responses of an otherwise homogeneous group of subjects. Implementation of strict subject selection criteria including restrictions on age and sex in most of the studies narrowed only slightly the distribution of responses. Attempts to determine predisposing factors responsible for increased or decreased O_3 responsiveness utilizing nonspecific tests were unsuccessful (Hazucha, 1981). Individual responsiveness is probably a function of many factors. Previous exposures of individuals to other pollutants (Hackney et al., 1976, 1977b), and nutritional deficiencies and/or latent infection(s), known to be relevant in animals (Chapter 9), might be among contributing factors. Individual responsiveness appears to be maintained relatively unchanged for as long as 10 months. Generally, within-individual variability in response is considerably smaller than the variations reported between subjects (McDonnell et al., 1985a; Gliner et al., 1983).

In studies that have described the distribution of individual responses to ozone (McDonnell et al., 1983; Kulle et al., 1985), the changes in pulmonary function resulting from exposure to clean air or near zero ozone concentrations are small and uniformly distributed. As the ozone concentration increases, the distribution widens and becomes skewed towards larger decrements in pulmonary function, the largest changes respresenting the most responsive subjects. Reported retrospective classification of subjects into "responders/sensitives" and "nonresponders/nonsensitives" varies from study to study. Some subjects were classified as "responders" by medical history and previous exposures or test results, or both (Hackney et al., 1975); others had to show more than 10 percent post-exposure decrements (Horvath et al., 1981) or decrements exceeding two standard deviations of the control (Haak et al., 1984). The term "hyperreactor" or "hyperresponder" has been arbitrarily used to describe the 5 to 20 percent of the population that is most responsive to ozone exposure. There are no clearly established criteria for defining "reactive" or "nonreactive" subjects. Nevertheless, it is important to identify criteria to define the "reactive" portion of the population since they may represent a subgroup of the population which can be considered "at risk".

Intermittent exercise augments physiological response to O_3. Moderate exercise ($\dot{V}_E$ = 24-43 L/min) in 0.4 ppm ozone for 2 hr reduced the FEV_1 of healthy subjects by an average of 11 percent. In contrast, rest under the same environmental conditions decreased FEV_1 by only 3 percent (Haak et al., 1984), while very heavy exercise ($\dot{V}_E > 64$ L/min) reduced FEV_1 by 17 percent on the average (5 to 50 percent) (McDonnell et al., 1983). Even low O_3 concentrations (0.12 ppm) induced measurable changes in the lung function of more responsive individuals; the average decrements in FVC, FEV_1, and FEF_{25-75} were 3, 4.5, and 7.2 percent from control, respectively (McDonnell et al., 1983). The maximum changes were observed within 5 to 10 minutes following the end of each exercise period (Haak et al., 1984). During subsequent rest periods, however, the response does not persist and partial improvement in lung function can be observed despite continuous inhalation of ozone (Folinsbee et al., 1977b). Functional recovery from a single exposure with exercise appears to progress in two phases: during the initial rapid phase, lasting between 30 min and 3 hr, improvement in lung function exceeds 50 percent; this is followed by a much slower recovery phase usually completed in most subjects within 24 hr (Bates and Hazucha, 1973). There are some individuals, however, whose lung function did not reach the pre-exposure level even after 24 hrs. Despite apparent functional recovery of most of the subjects, an enhanced responsiveness to a second O_3 challenge may persist in some subjects for up to 48 hr (Bedi et al., 1985; Folinsbee and Horvath, 1986). In addition, other regulatory systems may still exhibit abnormal responses when stimulated; e.g., airway hyperreactivity may persist for days (Golden et al., 1978; Kulle et al., 1982b).

The magnitude of functional changes assessed by spirometry is positively associated with O_3 concentration. Exposure of intermittently exercising subjects ($\dot{V}_E$ > 63 L/min) for 2 hr to 0.4 ppm reduced significantly ($p < 0.005$) FVC by 12 percent, FEV_1 by 17 percent, and FEF_{25-75} by 27 percent on the average. At lower O_3 concentrations (0.18 to 0.24 ppm) the respective decrements (FVC 4 to 11 percent, FEV_1 6 to 14 percent, FEF_{25-75} 12 to 23 percent) were still statistically significant (McDonnell et al., 1983). The same ventilation in a 0.12 or 0.15 ppm O_3 atmosphere elicited spirometric changes (1 to 7 percent) of only questionable significance (McDonnell et al., 1983; Kulle et al., 1985).

Similar positive associations have been reported between lung function decrements and the level of ventilation. Intermittent exercise ($\dot{V}_E$ > 68 L/min) in 0.3 ppm O_3 decreased FVC, FEV_1, and FEF_{25-75} by 7, 8, and 10 percent, respectively. A lower intensity of exercise ($\dot{V}_E$ ~ 32 L/min) in the same O_3 atmosphere induced proportionally smaller changes; the respective mean decrements were 2, 5, and 8 percent (Folinsbee et al., 1978).

More recently, the relationship between ventilation, exposure time, O_3 concentration, and functional response has been examined in a more general way. The response has been evaluated as a function of an "effective rate" (Colucci, 1983), an "effective dose" (Colucci, 1983; Folinsbee et al., 1978; Silverman et al., 1976), and O_3 concentration (Kulle et al., 1985). The concept of defining ozone exposure in terms of an "effective dose" (the product of concentration, ventilation, and time) is relatively simple from a modeling point of view. A major weakness of this concept, however, is that the same dose/rate may induce quantitatively different responses, which limits the general applicability of the model for standard-setting (Silverman et al., 1976; Folinsbee et al., 1978). Moreover, the small data base(s) and the limited statistical evaluation of almost all of these models further precludes their quantitative applications and limits their qualitative application(s) to conditions similar to those for which the models were derived.

The effects of intermittent exercise and O_3 concentration on the magnitude of average pulmonary function responses (e.g., FEV_1) during 2-hr exposures are illustrated in Figures 12-2 through 12-5. The data sets on which the predictive models are based have been limited to studies utilizing intermittent exercise and 2-hr exposure protocols. The following types of data were included in the analysis: (1) data from single exposures; (2) data obtained on the first day of sequential, multiday exposures; and (3) data obtained from repetitive exposures of the same cohort to a range of concentrations or to the same concentration but with different levels of exercise, provided the reported exposures were each separated by at least 7 days. To minimize inhomogeneity of data further, studies conducted under unique environmental conditions (e.g., high relative humidity and temperature) or on known hyperreactive groups of subjects were not included in this analysis. Neither were data from resting and continuous exercise studies included in the calculations.

The selected set of 25 studies represents data obtained on 320 subjects studied between 1973 and 1985, in 8 different laboratories (Table 12-3). Since minute ventilation is one of the most important determinants of response to ozone, the data have been categorized by reference to exercise level, as defined by minute ventilation. Based on a distribution pattern of $\dot{V}_E$ during exercise, four subgroups were identified: light exercise ($\dot{V}_E \leq 23$ L/min), moderate ($\dot{V}_E = 24$ to 43 L/min), heavy ($\dot{V}_E = 44$ to 63 L/min), and very heavy exercise group ($\dot{V}_E \geq 64$ L/min). Although basic second-order functions were considered in modeling the concentration-response relationship, the pure quadratic function with no intercept was found to be the simplest and most suitable model since this is the only function that passes through a minimum (no response) at zero O_3 concentration. The relative contribution of each data point was adjusted by weighing it by the number of subjects. Scatter plots with superimposed best-fit curves and 95 percent confidence limits for FEV_1 at each exercise level show clearly differentiated response curves with high correlation coefficients ($r = 0.89$ to 0.97). A strong and statistically significant ($p < 0.0001$) positive association between decrements in FEV_1 and ozone concentration for all levels of exercise is apparent. From the curves, it can be determined with 95 percent confidence that light exercise in a 0.2 ppm O_3 atmosphere will decrease FEV_1 by 1.6 percent, moderate exercise by 2.4 percent, heavy exercise by 2.8 percent, and very heavy exercise by 4.7 percent on the average, respectively. Inversely, a 5 percent decrement in FEV_1 can be

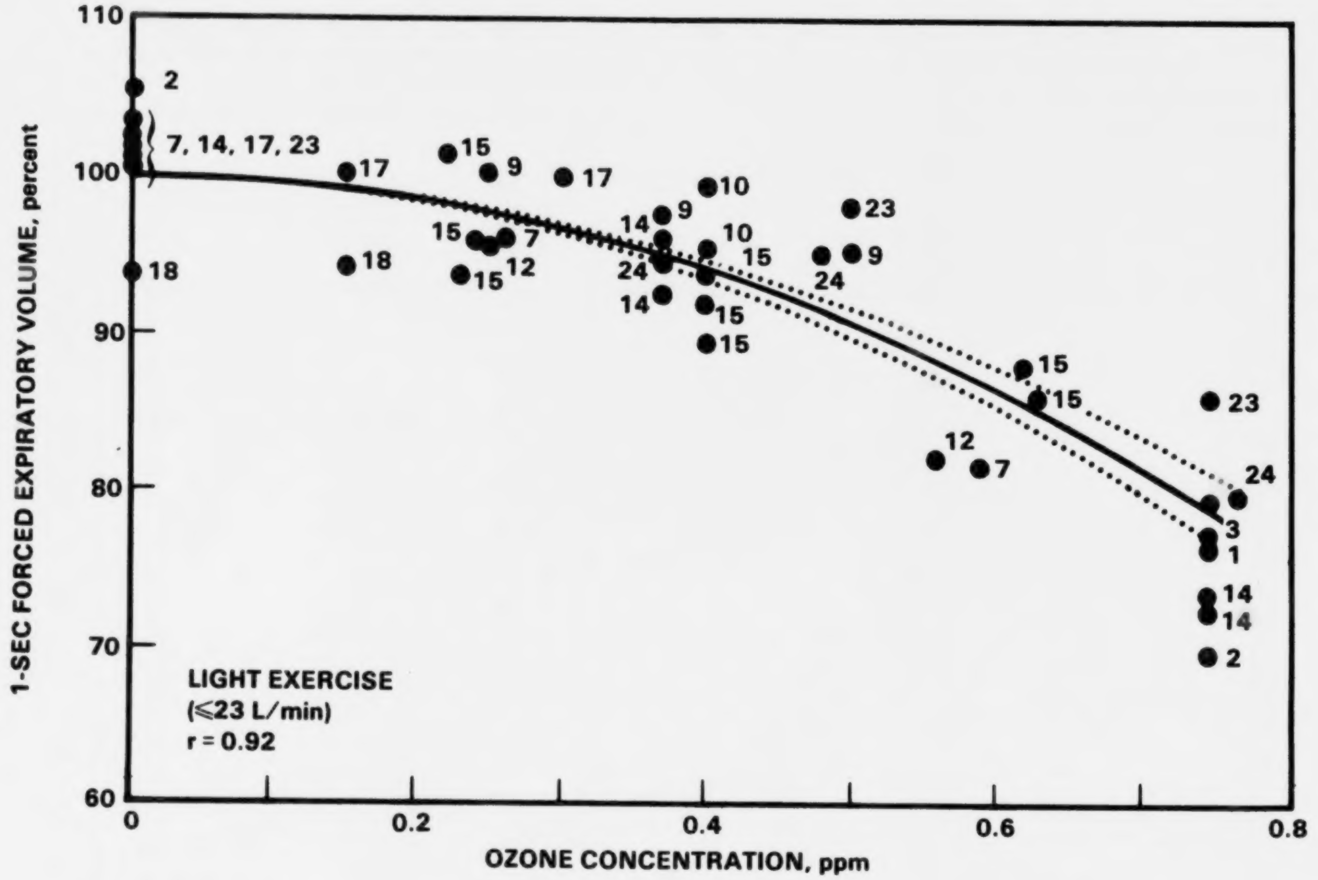

Figure 12-2. The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with light intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits. Individual means (± standard error) are given in Table 12-3 along with specific references.

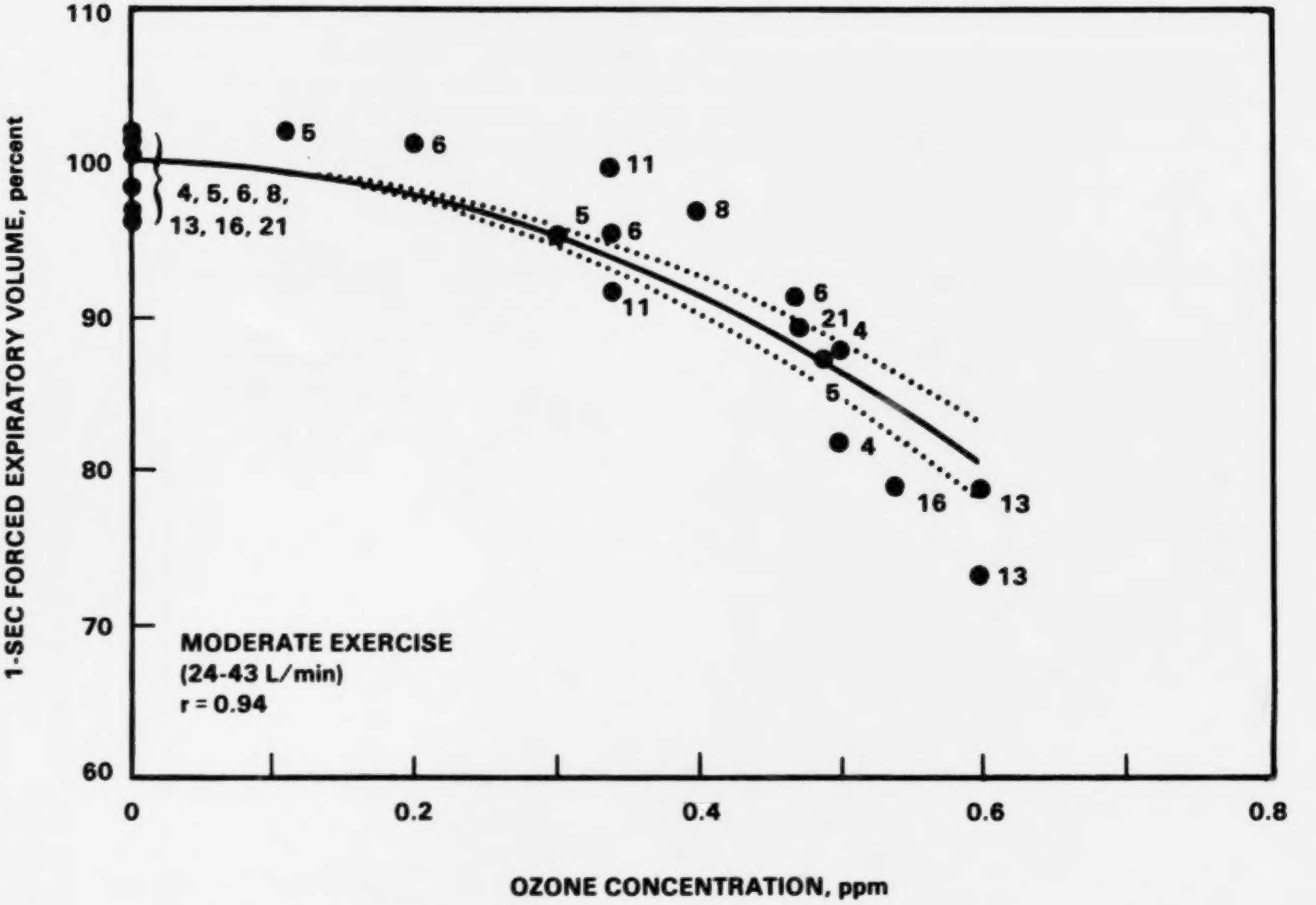

Figure 12-3. The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with moderate intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits. Individual means (± standard error) are given in Table 12-3 along with specific references.

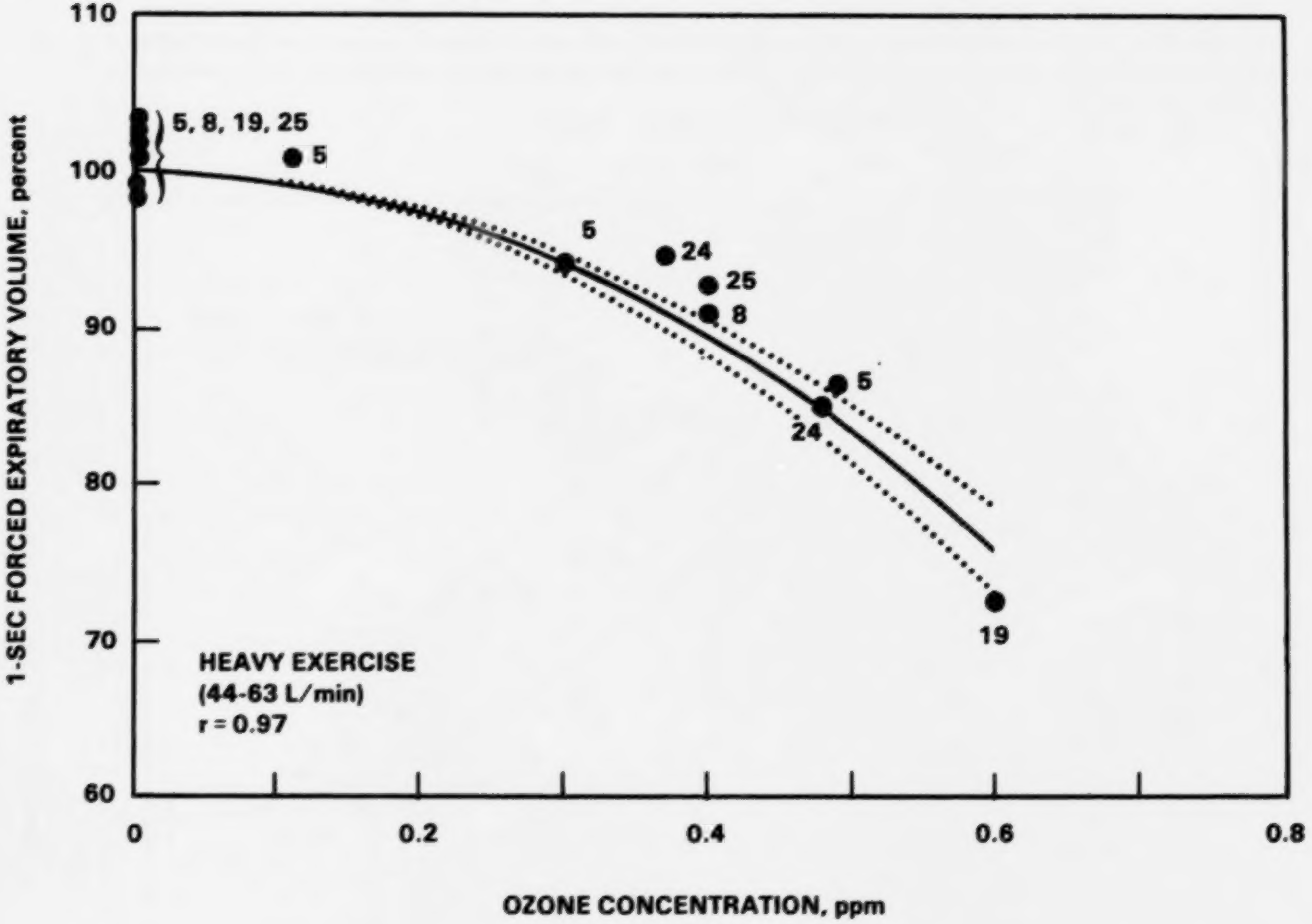

Figure 12-4. The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with heavy intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits. Individual means (± standard error) are given in Table 12-3 along with specific references.

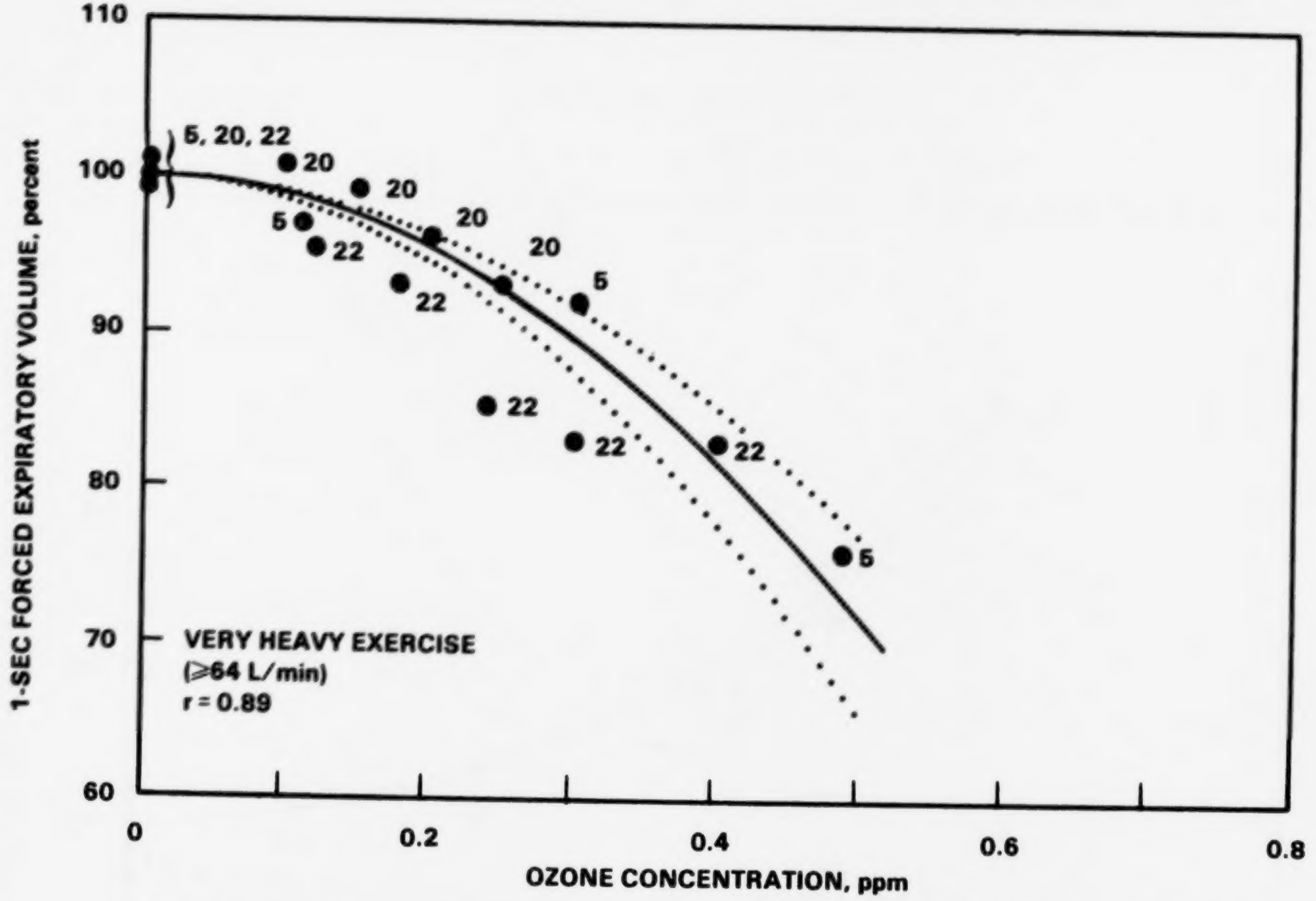

Figure 12-5. The effects of ozone concentration on 1-sec forced expiratory volume during 2-hr exposures with heavy intermittent exercise. Quadratic fit of group mean data, weighted by sample size, was used to plot a concentration-response curve with 95 percent confidence limits. Individual means (± standard error) are given in Table 12-3 along with specific references.

TABLE 12-3. EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME DURING 2-hr EXPOSURES

Ozone[a] concentration μg/m³	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$,[d] %	Reference[a]
LIGHT EXERCISE		($\dot{V}_E \leq 23$ L/min)					
1470	0.75	MAST, NBKI	120	10	22.5	79.3 ± 2.7	(1) Bates and Hazucha, 1973
1470	0.75		120	10	22.5	76.6 ± 2.7	
0	0.00	MAST, NBKI	120	3	23.0	104.9	(2) Bates et al., 1972
1470	0.75		120	3	23.0	69.7	
1470	0.75	CHEM, NBKI	120	11	20.0	77.2 ± 4.4	(3) Folinsbee et al., 1977a
0	0.00	CHEM, NBKI	125	21	22.6	100.3 ± 0.8	(7) Gliner et al., 1983
510	0.26		125	21	22.6	96.9 ± 1.3	
1156	0.59[e]		125	21	22.6	81.6 ± 2.7	
490	0.25	CHEM, NBKI	120	6	20.0	100.3	(9) Hackney et al., 1975
725	0.37		120	5	20.0	97.7	
980	0.50		120	7	20.0	95.3	
784	0.4	CHEM, NBKI	135	6	20.0	99.5	(10) Hackney et al., 1976
784	0.4		135	9	20.0	95.5	
490	0.25	MAST, NBKI	120	3	22.0	95.7 ± 4.1	(12) Hazucha, 1973
1098	0.56		120	3	22.0	82.1 ± 13.2	
0	0.00	MAST, NBKI	120	6	22.0	101.4 ± 1.7	(14) Hazucha et al., 1973
0	0.00		120	6	22.0	100.5 ± 3.3	
725	0.37		120	6	22.0	92.6 ± 2.3	
725	0.37		120	6	22.0	96.1 ± 0.7	
1470	0.75		120	6	22.0	73.3 ± 6.8	
1470	0.75		120	6	22.0	72.4 ± 4.7	

TABLE 12-3 (continued). EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME DURING 2-hr EXPOSURES

Ozone[a] concentration μg/m^3	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$,[d] %	Reference[a]
431	0.22	MAST, NBKI	120	4	22.5	101.5	(15) Hazucha et al., 1977
451	0.23		120	4	22.5	93.7 ± 1.4	
470	0.24		120	4	22.5	96.0 ± 3.1	
784	0.40		120	4	22.5	93.9 ± 2.5	
784	0.40		120	4	22.5	91.9 ± 5.9	
784	0.40		120	4	22.5	89.5	
1215	0.62		120	4	22.5	88.0	
1235	0.63		120	4	22.5	86.0	
0	0.00		120	15	22.0	100.9	(17) Kagawa, 1984
294	0.15		120	15	22.0	100.3	
588	0.30		120	10	22.0	100.1	
0	0.00		120	6	20.0	93.3	(18) Kagawa and Tsuru, 1979b
294	0.15		120	6	20.0	94.3	
0	0.00		120	8	22.5	102.8	(23) Shephard et al., 1983
0	0.00		120	8	22.5	101.9	
980	0.50		120	8	22.5	98.2	
1470	0.75		120	8	22.5	86.0	
725	0.37		120	5	22.5	94.6 ± 3.5	(24) Silverman et al., 1976
941	0.48		120	5	22.5	95.1 ± 1.9	
1509	0.77		120	5	22.5	79.8 ± 6.4	

TABLE 12-3 (continued). EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME DURING 2-hr EXPOSURES

Ozone[a] concentration µg/m^3	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	FEV$_{1.0}$,[d] %	Reference[a]
MODERATE EXERCISE ($\dot{V}_E$ = 24-43 L/min)							
0	0.0	CHEM, NBKI	118	8	36.0	99.4 ± 2.7	(4) Folinsbee et al., 1977b
0	0.0		118	6	35.0	96.4 ± 5.5	
980	0.5		118	8	33.3	87.8 ± 6.4	
980	0.5		118	6	39.2	81.9 ± 5.6	
0	0.00	CHEM, NBKI	120	10	32.6	99.4 ± 13.1	(5) Folinsbee et al., 1978
216	0.11		120	10	32.3	101.9 ± 13.8	
588	0.30		120	10	31.0	95.4 ± 16.0	
960	0.49		120	10	32.1	87.3 ± 16.6	
0	0.00	CHEM, NBKI	135	10	32.0	99.6 ± 4.3	(6) Folinsbee et al., 1980
0	0.00		135	10	30.0	100.6 ± 4.7	
0	0.00		135	10	31.0	100.2 ± 5.1	
392	0.20		135	10	31.0	101.3 ± 4.8	
666	0.34		135	10	32.0	95.5 ± 4.3	
921	0.47		135	10	30.0	91.3 ± 5.0	
0	0.0	CHEM, GPT	120	29	35.0	101.5 ± 2.6	(8) Haak et al., 1984
0	0.0		120	15	35.0	99.7 ± 4.3	
784	0.4		120	15	35.0	96.9 ± 5.5	
666	0.34	CHEM, NBKI	120	4	24.0	91.7 ± 27.4	(11) Hackney et al., 1977b
666	0.34		120	4	24.0	99.7 ± 18.1	
0	0.0	CHEM, NBKI	120	14	35.0	97.9 ± 5.1	(13) Hazucha, 1981
0	0.0		120	14	35.0	96.0 ± 6.7	
1176	0.6		120	14	35.0	78.8 ± 6.1	
1176	0.6		120	14	35.0	73.1 ± 6.5	

TABLE 12-3 (continued). EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME DURING 2-hr EXPOSURES

Ozone[a] concentration µg/m³	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$,[d] %	Reference[a]
0	0.00	UV, UV	125	24	30.0	99.7 ± 1.0	(16) Horvath et al., 1981
1058	0.54		125	24	30.0	78.9 ± 3.0	
0	0.00	UV, NBKI	120	11	24.0	100.8	(21) Linn et al., 1982b
921	0.47		120	11	24.0	88.7	
HEAVY EXERCISE		($\dot{V}_E$ = 44-63 L/min)					
0	0.00	CHEM, NBKI	120	10	50.4	100.8 ± 16.3	(5) Folinsbee et al., 1978
196	0.11		120	10	49.8	100.5 ± 16.2	
588	0.30		120	10	56.3	93.7 ± 17.5	
980	0.49		120	10	51.4	85.8 ± 19.5	
0	0.0	CHEM, GPT	120	15	57.0	99.4 ± 5.0	(8) Haak et al., 1984
0	0.0		120	15	57.0	98.7 ± 4.1	
0	0.0		120	15	57.0	101.9 ± 4.3	
784	0.4		120	15	57.0	90.6 ± 4.9	
0	0.0	CHEM, NBKI	120	20	45.0	102.5	(19) Ketcham et al., 1977
1176	0.6		120	20	45.0	71.6	
725	0.37	MAST, NBKI	120	5	46.5	94.3	(24) Silverman et al., 1976
941	0.48		120	5	44.7	84.4	
0	0.0	CHEM, NBKI	120	10	55.3	98.8 ± 5.6	(25) Stacy et al., 1983
784	0.4		120	12	55.3	92.3 ± 4.8	

TABLE 12-3 (continued). EFFECTS OF INTERMITTENT EXERCISE AND OZONE CONCENTRATION ON 1-SEC FORCED EXPIRATORY VOLUME DURING 2-hr EXPOSURES

Ozone[a] concentration µg/m³	Ozone[a] concentration ppm	Measurement[b,c] method	Exposure duration, min	Number of subjects	Minute ventilation, L/min	$FEV_{1.0}$,[d] %	Reference[a]
VERY HEAVY EXERCISE ($\dot{V}_E \geq 64$ L/min)							
0	0.00	CHEM, NBKI	120	10	66.8	99.7 ± 13.7	(5) Folinsbee et al., 1978
216	0.11		120	10	71.2	97.4 ± 17.6	
588	0.30		120	10	68.4	92.3 ± 12.7	
960	0.49		120	10	67.3	76.1 ± 11.9	
0	0.00	CHEM, UV	125	22	66.2	98.9 ± 2.4	(22) McDonnell et al., 1983
235	0.12		125	22	68.0	95.7 ± 3.2	
353	0.18		125	20	64.6	93.6 ± 3.4	
470	0.24		125	21	64.9	85.6 ± 3.4	
588	0.30		125	21	65.4	83.2 ± 3.8	
784	0.40		125	29	64.3	83.0 ± 3.7	
0	0.0	UV, UV	113	20	70	101.3	(20) Kulle et al., 1985
196	0.10		113	20	70	101.0	
294	0.15		113	20	70	99.4	
392	0.20		113	20	70	96.7	
490	0.25		113	20	70	93.3	

[a] References are listed alphabetically within each exercise category; reference number refers to data points on Figures 12-2 through 12-5.

[b] Measurement method: MAST = KI-coulometric (Mast meter); CHEM = gas-phase chemiluminescence; UV = ultraviolet photometry.

[c] Calibration method: NBKI = neutral buffered potassium iodide; GPT = gas phase titration; UV = ultraviolet photometry.

[d] Data reported as mean ± standard error of the mean; not all references provided standard errors.

[e] Subjects exposed to 0.55 and 0.65 ppm ozone were reported as one group (Gliner et al., 1983).

expected with light exercise in 0.36 ppm O_3, moderate exercise in 0.29 ppm O_3, heavy exercise in 0.27 ppm O_3, and very heavy exercise in a 0.21-ppm O_3 atmosphere. Since the models are based on a large number of data and show highly statistically significant differences of slope with narrow confidence bands, they are acceptable for quantitative estimates of response. It is important to note, however, that any predictions of average pulmonary function responses to O_3 only apply under the specific set of exposure conditions at which these data were derived. Other pulmonary function variables analyzed in the same manner, although not illustrated here, showed the same trend as the FEV_1, but as expected, changes differed in magnitude. For example, the decrements in FVC were smaller, while decrements in FEF_{25-75} were greater, for a given O_3 concentration, than decrements in FEV_1. The R_{aw} showed a similar concentration-dependent, positively correlated response ($r = 0.73$).

Continuous exercise equivalent in duration to the sum of intermittent exercise periods at comparable ozone concentrations and minute ventilation ($\dot{V}_E$ >60 L/min) elicited greater changes in pulmonary function. The enhancement ranged from several percent to more than a twofold augmentation of the effects (Folinsbee et al., 1984; Avol et al., 1984, 1985c). Others, on the other hand, have reported group mean responses in continuous exercise exposures that were similar to those previously observed with comparable levels of intermittent exercise (Adams et al., 1981; Adams and Schelegle, 1984). The lack of sufficient data, however, on comparable levels of exercise in the same subjects prevents any quantitative comparison of the effects induced by continuous versus intermittent exercise.

Exercise not only stresses the respiratory system but other physiological systems, as well, particularly the cardiovascular and musculoskeletal systems. Various compensatory mechanisms activated within these systems during physical activity might facilitate, suppress, or otherwise modify the magnitude and persistence of the reaction to ozone. Unfortunately, to date only a few of the studies were specifically designed to examine nonpulmonary effects of exercise in ozone atmospheres (Gliner et al., 1975, 1979). In one study, light intermittent exercise ($\dot{V}_E$ = 20-25 L/min) at a high ozone concentration (0.75 ppm) reduced post-exposure maximal exercise capacity by limiting maximal oxygen consumption (Folinsbee et al., 1977a); submaximal oxygen consumption changes were not significant (Folinsbee et al., 1975). The extent of ventilatory (V_T, f_R) and respiratory metabolic changes ($\dot{V}O_2$) observed during or following the exposure appears to have been related to the magnitude of pulmonary function impairment. Whether such (metabolic) changes are consequent to respiratory discomfort or are the result of changes in lung mechanics, or both, is still unclear and needs to be elucidated.

12.3.2.3 Environmental Stresses. Environmental conditions such as heat and relative humidity (rh) may contribute to symptoms and physiological impairment during and following O_3 exposure. A hot (31 to 40°C) and/or humid (85 percent rh) environment, combined with exercise in the O_3 atmosphere, has been shown to reduce forced expiratory volume more than similar exposures at normal room temperature and humidity (25°C, 50 percent rh) (Folinsbee et al., 1977b; Gibbons and Adams, 1984). Modification of the effects of O_3 by heat or humidity stress may be attributed to increased ventilation associated with elevated body temperature but there may also be an independent effect of elevated body temperature on pulmonary function (e.g., VC).

12.3.3 Other Factors Affecting Pulmonary Response to Ozone

12.3.3.1 Age. Although age has been postulated as a factor capable of modifying responsiveness to O_3, studies have not been designed to test specifically for the effects of age on responsiveness to O_3. Epidemiological studies in both children and young adults have suggested an association between decreased lung function and exposure to oxidant-polluted ambient air but no comparisons were made in these studies between different age groups (Lippmann et al., 1983; Lebowitz et al., 1982, 1983, 1985; Lebowitz, 1984; Bock et al., 1985; Lioy et al., 1985). In addition, it is not clear if the observed effects are attributable to O_3 alone since these studies have considerable methodological problems, including the inability to adjust adequately for the confounding influence of other pollutants and environmental conditions in ambient air (see Chapter 11). Controlled-exposure studies, however, on children and adolescents exposed to O_3 or ambient air containing predominantly O_3 (Avol et al., 1985a,b; McDonnell et al., 1985b,c) have indicated that the effects of O_3 on lung spirometry were very similar to those found in adults exposed under similar conditions, except that no significant increases in symptoms were found in children. Therefore, based on the limited pulmonary function data available, young children and adolescents do not appear to respond any differently to O_3 than adults. Further research is needed to confirm these preliminary findings in the young and also to determine if older subjects have altered responsiveness to O_3.

As with human studies to date, the influence of age on responsiveness to ozone is also difficult to assess from animal studies. Very few age comparisons have been made within a single study. Raub et al. (1983), Barry et al. (1983), and Crapo et al. (1984) studied pulmonary function and morphometry of the proximal alveolar region in neonatal (1-day-old) and young adult (6-week-old) rats exposed to 0.08, 0.12, or 0.25 ppm ozone for 12 hr/day, 7 days/week for 6 weeks. A few different responses were observed in the neonates and adults, but they were not major. Generally, neonates and young adults were about equally responsive, which is consistent with the human studies summarized above.

Animal studies of lung antioxidant metabolism and oxygen consumption (Lunan et al., 1977; Tyson et al., 1982; Elsayed et al., 1982) indicate that the stage of development at initiation of short-term exposure determines the response to O_3. Generally, the direction of the effect differs before and after weaning. Suckling neonates (5 to 20 days old) exhibited a decrease in antioxidant enzyme activities; as the animals grew older (up to 180 days old), enzyme activities increased progressively, reached a plateau at 35 days of age, and persisted after cessation of exposure. This biochemical response may be attributed to morphological changes in the lung that have a similar age-related pattern in the progression of centriacinar lesions in rats exposed to O_3 before and after weaning (Stephens et al., 1978). Thus, further research is needed to determine if the young differ markedly from adults in their response to O_3.

12.3.3.2 Sex. Sex differences in responsiveness to ozone have not been adequately studied. A small number of female subjects have been exposed to O_3 in mixed cohorts in many human controlled studies, but only three reports gave enough information for a limited comparative evaluation (Horvath et al., 1979; Gliner et al., 1983; DeLucia et al., 1983). Two additional studies (Gibbons and Adams, 1984; Lauritzen and Adams, 1985) compared O_3 effects in women with the results from male subjects previously studied in the same laboratory. The studies reported above suggest that lung function of women, as assessed by changes in $FEV_{1.0}$, may have been affected more than that of men under similar exercise and exposure conditions, but the results are not conclusive. Field and epidemiological studies of children and adolescents exposed to ambient air have also tended to show greater effects in girls, but the differences either were not tested statistically (Bock et al., 1985) or were not significant

(Avol et al., 1985a,b). Further research is needed to determine whether systematic differences exist between the sexes in their responses to ozone and what factors might be responsible for those differences.

The majority of animal studies have been conducted with male animals. Generally, when females have been used they have not been compared to males in the same study. This makes comparisons from animal data of sex-related differences in sensitivity to ozone virtually impossible. The only exception is a study of effects of ozone in increasing pentobarbital-induced sleeping time (Graham et al., 1981). Since waking from pentobarbital anesthesia is brought about by xenobiotic metabolism in the liver, this effect is considered to be extrapulmonary. Both sexes of mice, rats, and hamsters were exposed to 1 ppm ozone for 5 hr. Increased sleeping time was observed in all females, but not in male mice or male rats. Male hamsters were affected, but significantly less than the females. The reasons for this sex difference are unknown. Rats have major sex differences in xenobiotic metabolism, but the other species do not.

12.3.3.3 Smoking Status. Differences between smokers and nonsmokers have been studied often, but the smoking histories of subjects are not documented well. Hazucha et al. (1973) and Bates and Hazucha (1973) appear to have demonstrated greater responses (FVC, MMFR) in nonsmokers at 0.37 ppm O_3, but the responsiveness was reversed at 0.75 ppm (RV, FEV_1, $\dot{V}_{max50}$, and MMFR). Kerr et al. (1975) observed greater responses (FVC, SG_{aw}, R_L, FEV_3, and symptoms) in nonsmokers at 0.5 ppm O_3 for 6 hr. DeLucia et al. (1983) also observed greater responses in nonsmokers for VC, FEV_1, MMFR, f_B, and V_T at 0.3 ppm O_3 (1 hr). Kagawa and Tsuru (1979a) found greater effects of ozone among nonsmokers at 0.5 ppm than at 0.3 ppm O_3 (2 hr); a later study (Kagawa, 1983) showed that nonsmokers also had a greater response (SG_{aw}) than smokers to 0.15 ppm (2 hr). Shephard et al. (1983) found a slower and smaller change in spirometric variables in smokers at 0.5 and 0.75 ppm (2 hr). While none of these controlled studies examined the effects of different degrees of smoking, the general trend suggests that smokers are less responsive than nonsmokers. The reasons for these differences are not known; however, smokers have altered lung function and an increase in mucus, both of which could influence the dosimetry of O_3 in respective regions of the lung.

12.3.3.4 Nutritional Status. Posin et al. (1979) found that human volunteers receiving 800 (about four times the recommended daily units) or 1600 IU of vitamin E for 9 weeks as a supplement showed no differences in blood biochemistry from unsupplemented volunteers when exposed to 0.5 ppm ozone for 2 hr. The biochemical parameters studied included red cell fragility, hematocrit, hemoglobin, glutathione concentration, and activities of acetylcholinesterase, glucose-6-phosphate dehydrogenase, and lactic acid dehydrogenase. No differences in pulmonary function and symptoms were found between the vitamin E-supplemented and placebo groups (Hackney et al., 1981).

Hamburger et al. (1979) studied the effects of ozone exposure on the agglutination of human erythrocytes by the lectin concanavalin A. Pre-incubation with malonaldehyde, an oxidation product of polyunsaturated fatty acids, decreased concanavalin A agglutination of red cells exposed in vitro to ozone. Red cells obtained from 29 subjects receiving 800 IU of vitamin E or a placebo were exposed to 0.5 ppm ozone for 2 hr. Following ozone exposure, a slight decrease in agglutination occurred in cells from subjects who did not receive vitamin E supplementation, but the results were not statistically significant.

Increased activity of the glutathione peroxidase system may be one of the most sensitive, biochemically measured indices of exposure to $\leq$ 1 ppm of O_3 because it is involved in antioxidant metabolism. Increases in the activity of the glutathione peroxidase system have been reported after exposure of rats on a vitamin E-deficient diet to levels as low as 0.1 ppm O_3 for 7 days (Chow et al., 1981; Mustafa, 1975; Mustafa and Lee, 1976). The amount of dietary vitamin E fed to the rats influenced the ozone-induced increase in this system. For example, when the diet of rats contained 66 ppm of vitamin E, increased glutathione peroxidase activity was observed at 0.2 ppm of O_3; with 11 ppm of vitamin E, increases occurred at 0.1 ppm (Mustafa and Lee, 1976). Several other investigators have shown that vitamin E deficiency in rats makes them more susceptible to these ozone-induced enzymatic changes (Chow et al., 1981; Plopper et al., 1979; Chow and Tappel, 1972).

Studies of ozone-exposed vitamin E-deficient or supplemented rats have been undertaken to correlate biochemical findings with morphological alterations. Rats maintained on a basal vitamin E diet had the typical centriacinar lesions found as a result of O_3 exposure (Stephens et al., 1974; Schwartz et al., 1976). Lesions were generally worse, however, in vitamin E-deficient or marginally supplemented rats compared to highly supplemented rats (Plopper et al., 1979; Chow et al., 1981), supporting the finding from mortality (Donovan et al., 1977) and biochemical studies that vitamin E is protective in rats.

The difference in response between animals and man with regard to the protective effects of vitamin E against ozone toxicity may lie in the pharmacokinetics of vitamin E distribution in the body. Redistribution of vitamin E from extrapulmonary stores to the lung is slow. Short exposures to ozone may not allow adequate time for redistribution and for a protective effect to be observed. Animal exposures in which the striking effects of vitamin E on ozone toxicity were observed were generally conducted over longer exposure periods (often 1 to 2 weeks). Human subjects were exposed for shorter times and lower concentrations because of ethical considerations. Thus, vitamin E may have protective effects in man, but if they occur their demonstration might require longer exposure times and higher ozone concentrations. In animal studies, vitamin E-deficient rats are subject to increased toxicity from O_3 compared to supplemented groups, while animals on basal vitamin E diets are afforded little if any protection from O_3. In human studies, subjects were not likely to have had a deficiency substantial enough to show any effect. Thus, no evidence indicates that man would benefit from increased vitamin E intake relative to ambient ozone exposures, even though the antioxidant role of vitamin E in preventing ozone-initiated peroxidation _in vitro_ is well demonstrated and the protective effects _in vivo_ are clearly demonstrated in rats and mice. Further, vitamin E protection is not absolute and can be overcome by continued ozone exposure. The effects of vitamin E do support the general idea, however, that lipid peroxidation is involved in ozone toxicity.

12.3.3.5 _Red Blood Cell Enzyme Deficiencies_. The enzyme glucose-6-phosphate dehydrogenase (G-6-PD) is essential for the functioning of the glutathione peroxidase system in the red blood cell (RBC), which is the enzyme system proposed as having an integral part in the decomposition of fatty acid peroxides or hydrogen peroxide formed by O_3-initiated polyunsaturated fatty acid peroxidation (see Section 12.5.1). Therefore, Calabrese et al. (1977) have postulated that individuals with a hereditary deficiency of G-6-PD could possibly experience significant hematological effects from O_3 exposure. There have been too few studies performed, however, to reliably document this possibility. Most ozone studies have been with red blood cells from rodents, even though differences may exist between rodent and human RBCs. Calabrese and Moore (1980) and Moore et al. (1981) have pointed out the lack of ascorbic acid synthesis and the relatively low level of glucose-6-phosphate dehydrogenase (G-6-PD) in man compared to active ascorbic acid synthesis and high levels of G-6-PD in mice and rats. Although their species comparisons are based on a very limited data base, the authors point out the importance of developing animal models that can accurately predict the response of G-6-PD-deficient humans to oxidants such as O_3. This group has suggested the use of the C57L/J strain of mice and the Dorset sheep as better animal models for hematological studies since these species have levels of G-6-PD closer to those in man, especially those levels found in G-6-PD-deficient patients. The RBCs of Dorset sheep, however, appear to be no more sensitive to ozone than normal human RBCs, even though the G-6-PD levels in Dorset sheep are very low. Additional *in vitro* studies (Calabrese et al., 1982, 1983; Williams et al., 1983a,b,c) have demonstrated that the responses of sheep and normal human RBCs responded quite similarly when separately incubated with potentially toxic O_3 intermediates, but that G-6-PD-deficient human RBCs were considerably more susceptible. Even if O_3 or a reactive product of O_3-tissue interaction were to penetrate the RBC after *in vivo* exposure, it is unlikely that decrements in reduced glutathione activity would be large enough to lead to chronic hemolytic anemia in the affected individual.

12.3.4 Effects of Repeated Exposure to Ozone

12.3.4.1 *Introduction*. The attenuation of response associated with repeated exposure to O_3 is generally referred to as "adaptation." Earlier work in animals that focused primarily on reductions in pulmonary edema and mortality rate to assess this process employed the term "tolerance"; other terms have also been used to describe this phenomenon (Chapter 9, Section 9.3.5). The distinction, if any, among these terms with respect to O_3 and its effects has never been established in a clear, consistent manner.

The following sections describe the nature of observed alterations in responsiveness to O_3 and discuss possible interrelationships for those observed changes in responsiveness.

12.3.4.2 *Development of Altered Responsiveness to Ozone*. Successive daily brief exposures of human subjects to O_3 (< 0.7 ppm for ~ 2 hrs) induce a typical temporal pattern of response (Chapter 10, Section 10.3). Maximum functional changes that occur on the first exposure day, as assessed by plethysmographic and bronchial reactivity tests (Farrell et al., 1979; Dimeo et al., 1981), or on the second exposure day, as assessed by spirometry, become progressively attenuated on each of the subsequent days (Horvath et al., 1981; Kulle et al., 1982b; Linn et al., 1982b). By the fourth day of exposure, the average effects are not different from those observed following control (air) exposure. Individuals need between 3 and 7 days of exposure to develop full attenuation, with more sensitive subjects requiring more time (Horvath et al., 1981; Kulle et al., 1982b; Linn et al., 1982b; Haak et al., 1984). The magnitude of a peak response appears to be directly related to O_3 concentration (Folinsbee et al., 1980; Haak et al., 1984). Whether varying the length or the frequency of exposure will modify the time course of this altered responsiveness has not been explored. Full attenuation, even in ozone-sensitive subjects, does not persist for more than 3 to 7 days after exposure in most individuals (Horvath et al., 1981; Kulle et al., 1982b; Linn et al., 1982b), while partial attenuation might persist for up to 2 weeks (Horvath et al., 1981). Although the severity of symptoms generally correlates with the magnitude of the functional response, partial attenuation of symptoms appears to persist longer, for up to 4 weeks after exposure (Linn et al., 1982b). Ozone concentrations inducing few or no functional effects ($\leq$ 0.2 ppm) elicited no significant changes in pulmonary function with consecutive exposures (Folinsbee et al., 1980). The latter findings are consistent with the proposition that functional attenuation may not occur in the airways of individuals living in communities where the ambient ozone levels do not exceed 0.2 ppm. The difficulty, however, of drawing such inferences on the basis of narrowly defined laboratory studies is that under ambient conditions a number of uncontrollable factors might modify the response. Most notably, other pollutants may interact with ozone during more protracted ambient exposures to induce changes at concentrations lower than those reported from controlled-laboratory studies. The evidence suggesting that Los Angeles residents exhibit functional attenuation of the response to O_3 is sparse (Hackney et al., 1976, 1977a,b; Linn et al., 1983a) and requires confirmation.

12.3.4.3 Conclusions Relative to Attenuation with Repeated Exposures. The attenuation of acute effects of O_3 after repeated exposure, such as changes in lung function, have been well documented in controlled human exposure studies. There are no practical means at present, however, of assessing the role of altered responsiveness to O_3 in human populations chronically exposed to ozone. No epidemiological studies have been designed to test whether attenuation of symptoms, pulmonary function, or morbidity occurs in association with photochemical air pollution. It might be added that the proposition would be difficult to test epidemiologically. Thus, scientists must rely mainly on inferences and qualitative extrapolations from animal experimentation.

Attenuation of response to O_3 may be viewed as a process exhibiting some concentration-response characteristics. Concentrations of O_3 that have little or no effect do not appear to influence measurably the response invoked by subsequent exposures to higher O_3 concentrations. Over some higher range (0.2 to 0.8 ppm) of exposure, functional recovery after repeated exposure is virtually complete within several days. Insofar as this generalization is valid, it suggests that photochemical air pollution may induce altered responses only in individuals who previously responded to exposure. Above this range, persistent or progressive damage is most likely to accompany repeated exposure. The attenuation, however, of the functional changes (and the time course of attenuation) following repeated exposure to O_3 does not necessarily follow the morphological or biochemical pattern of responses nor does it necessarily imply that there is attenuation of the morphological or biochemical responses to O_3.

Responses to O_3, whether functional, biochemical, or morphological, have the potential for undergoing changes during repeated or continuous exposure. There is an interplay between tissue inflammation, hyperresponsiveness, ensuing injury (damage), repair processes, and changes in response. The initial response followed by its attenuation may be viewed either as sequential states in a continuing process of lung injury and repair or as a physiological adaptation to the irritative stimulus.

12.3.5 Mechanisms of Responsiveness to Ozone

The time course, type, and consistency of changes of such indices as symptoms, lung volumes, flows, resistances, and bronchial reactivity strongly implicate vagal sensory receptors as substantial modulators of responsiveness to O_3.

A growing body of evidence from both animal (Roum and Murlas, 1984; Lee et al., 1979; Gertner et al., 1983a,b) and human studies (Golden et al., 1978; DiMeo et al., 1981; Beckett et al., 1985) indicates that a post-ozone exposure increase in bronchial smooth muscle tone is mediated, at least in part, by increased tonic vagal activity consequent to stimulation of muscarinic receptors. Beckett et al. (1985) demonstrated that pretreatment of subjects with atropine (a bronchodilator and muscarinic, cholinergic blocker) prevented an increase in SR_{aw} and partially blocked a decrease in FEV_1; both tests are used clinically as indirect indices of bronchoconstriction. Atropine did not, however, prevent the reduction in FVC, increase in frequency of breathing (f_B), or decrease in tidal volume (V_T). Inhalation of other types of bronchodilators (e.g., isoproterenol, metaproterenol; adrenergic receptor agonists) immediately post-exposure relaxed constricted airways, while elevated R_{aw} and SR_{aw} returned rapidly to baseline values (Golden et al., 1978; Beckett et al., 1985). Such a pattern of response strongly suggests the involvement of vagal sensory receptors (irritant, stretch and J-receptors), since stimulation of these receptors will generally elevate bronchomotor tone, increase f_B, and decrease V_T. These findings show that ozone-induced increases in airway resistance are caused primarily by a reflex constriction of airway smooth muscle. The afferent pathways of this reflex originate at different receptor sites, but the (increased) efferent activity seems to be vagally mediated. Besides direct excitation of afferent end-organs (receptors, nerve endings), other factors may influence this (afferent) discharge. Enhanced sensitivity of receptors (Lee et al., 1977) and mucosal inflammation (Holtzman et al., 1983a,b), leading to increased epithelial permeability of bronchodilators (Davis et al., 1980), are some of the proposed mechanisms. Relative to effectors, sensitization of muscarinic receptors (Roum and Murlas, 1984) and mucosal hypersecretion may be contributing factors.

Under most circumstances, increased R_{aw} may be expected to reduce FVC and increase RV. The lack, however, of a significant association between individual changes in R_{aw} and FVC (McDonnell et al., 1983), and the disparate effects of bronchodilator agents on airway diameter, indicate the presence of more than one mechanism for O_3-induced changes in pulmonary function. At O_3 concentrations of 0.5 ppm and less, decrements in FVC have been related to decreases in TLC without changes in RV or TGV (Hackney et al., 1975; Folinsbee et al., 1977b, 1978; Kulle et al., 1985). The consequent decrease in TLC most likely results from inhibition of maximal inspiration, as indicated by the reduced IC reported at higher (0.75 ppm) O_3 concentrations (Bates et al., 1972). Whether such an inhibition of maximal inspiration is voluntary (due to discomfort) or involuntary (due to reflex pathways or altered lung mechanics) is unclear and awaits further experimentation. It is highly probable, however, that most of the decrements in lung volume reported to result from exposure to O_3 at concentrations of greatest relevance to standard-setting ($\leq$ 0.3 ppm) are caused by the inhibition of full inspiration rather than by changes in airway diameter. The lack of any reported changes in the FEV_1/FVC ratio also supports the restrictive nature of this mechanism (Farrell et al., 1979; Kagawa, 1984).

Among the non-vagal components of the functional response, the release of mediators is one of more plausible mechanisms suggested (Lee et al., 1979). None of the experimental evidence, however, is definitive. Additional investigation is needed to elucidate, assess the relative importance of, and determine the overall contribution of the mechanisms associated with ozone exposure.

Recent experiments by Gertner et al. (1983a,b,c) may provide additional information on possible mechanisms. They demonstrated that even a brief exposure of the peripheral airways of dogs to ozone triggered a functional response that, depending on O_3 concentration, could be mediated through reflex or humoral pathways, or both. The reflex-mediated response was subject to attenuation after repeated exposure, whereas the response mediated humorally was not.

Experimental evidence in laboratory animals also suggests a close relationship between the cellular response to O_3-induced injury, as measured by the appearance of neutrophils in the airway epithelium of dogs exposed to O_3, and airway hyperresponsiveness, as determined with a provocative aerosol (Holtzman et al., 1983a,b; Fabbri et al., 1984; Sielczak et al., 1983). When mobilization of the neutrophils was prevented by prior treatment with hydroxyurea (O'Byrne et al., 1983), the (neutrophilic) infiltration after ozone exposure was depressed (Fabbri et al., 1983), and no increase was seen in airway responsiveness.

Ozone toxicity, in both humans and laboratory animals, may be mitigated through altered responses at the cellular or subcellular level, or both. At present, the mechanisms underlying altered responses are unclear and the effectiveness of such mitigating factors in protecting the long-term health of the individual against O_3 is still uncertain (Bromberg and Hazucha, 1982). Since cellular mechanisms are difficult if not impossible to investigate in humans, animal studies become essential for identifying potential mechanisms of effects. Numerous basic metabolic processes in humans and animals appear to be similar; mechanisms underlying these processes may indeed provide some clues on possible mechanisms in humans (Mustafa and Tierney, 1978; Boushey et al., 1980). It has been shown that human and animal leukocytes, alveolar macrophages, and neutrophils produce superoxide radicals not only as a product of a vital biological reduction of molecular oxygen but also as a result of stressful stimuli (Pick and Keisari, 1981). Excessive production of radicals without adequate scavenging will injure the supporting tissues, while the attenuation of response to successive stimuli suppresses the release of free oxygen radicals and depresses the chemotactic responsiveness of the cells (Mustafa and Tierney, 1978; Bhatnagar et al., 1983). Accumulation of inflammatory cells at the site of injury and subsequent release of proteases capable of degrading connective tissue may upset the protease-antiprotease balance critical for controlling the extent of inflammation and injury. Perturbation of lung collagen metabolism, seen in vivo in animals exposed to O_3 (see Section 9.3.3.6), could be involved in the inflammatory response. Furthermore, the attenuation of prolyl hydroxylase (a key enzyme in collagen synthesis) activity (Hussain et al., 1976a,b), and concurrent changes in the activity of superoxide dismutase, the enzyme that catalyzes the dismutation of the superoxide free radical (Bhatnagar et al., 1983), could be another important pathway to the development of changes in responsiveness to O_3. (However, even though the prolyl hydroxylase activity returns to control levels, the collagen produced through the original increase in metabolism remains). The glutathione peroxidase system also increases after O_3 exposure, thereby providing another line of defense against oxidant toxicity (Chow, 1976; Chow et al., 1976).

With time, there is a reduction in the intensity and a change in the composition of the inflammatory response. Partial remission occurs with continuous or intermittent exposure. There are no data, however, showing how important the timing and duration of the O_3 pulsations may be in influencing the induction and remission of the inflammatory reaction. The latter issue has potential significance for public health, since exposure to ambient air pollution is essentially intermittent. The timing and intensity of exposure to ozone within the community, and consequently the potential of such exposures for inducing altered responses, are likely to be highly variable. Differences within the population in patterns of activity and biological status may be expected to contribute to this variability.

12.3.6 Relationship Between Acute and Chronic Ozone Effects

Understanding the relationship between acute effects that follow O_3 exposure of man or animals and the effects that follow long-term exposures of man or animals is crucial to the evaluation of the full array of possible human health effects of oxidant pollutants. Most of the acute responses to O_3 described in animals and man tend to return toward control (filtered air) values with time after the exposure ends. While effects of longer periods of exposure have been documented in laboratory animals (Chapter 9), human beings have not undergone long-term exposures in laboratory studies because of ethical and logistical considerations. In fact, little is known about the long-term implications of acute damage or about the chronic effects in man of prolonged exposure to O_3.

With newer techniques, the pulmonary function of experimental animals can be more completely evaluated and correlated with biochemical and morphological parameters. Long-term exposure of rats to less than 1.0 ppm O_3 results in increased lung volume, especially at high transpulmonary pressures (Bartlett et al., 1974; Moore and Schwartz, 1981; Raub et al., 1983; Costa et al., 1983). Costa et al. (1983) also observed increased pulmonary resistance and, at low lung volumes, decreased maximum expiratory flows in rats exposed to 0.2 or 0.8 ppm O_3 6 hr/day, 5 days/week for 62 exposures. The latter change was related to decreased airway stiffness or to narrowing of the airway lumen. Raub et al. (1983), in neonatal rats exposed to 0.12 or 0.25 ppm O_3 12 hr/day for 42 days, observed significantly lower peak inspiratory flows during spontaneous respiration, in addition to the increased lung volumes noted above. While Yokoyama and Ichikawa (1974) did not find changes in lung static pressure-volume curves of rats exposed to 0.45 ppm O_3 6 hr/day, 6 days/week for 6 to 7 weeks, Martin et al. (1983) reported increased maximum extensibility of alveolar walls and increased fixed lung volumes following exposure of rabbits to 0.4 ppm O_3 7 hr/day, 5 days/week for 6 weeks.

Wegner (1982) studied pulmonary function in bonnet monkeys exposed to 0.64 ppm O_3 8 hr/day, 7 days/week for up to 1 year. After 6 months of exposure, significant increases in pulmonary resistance and in the frequency dependence of pulmonary compliance were reported. In the monkeys exposed for 1 year, Wegner (1982) reported significantly increased pulmonary resistance and inertance; and decreased flows during forced expiratory maneuvers at low lung volumes and decreased volume expired in 1 second (FEV_1). These findings were interpreted as indicating narrowing of the peripheral airways. This observation was confirmed, using morphometric techniques, by Fujinaka et al. (1985), who reported that respiratory bronchioles of the bonnet monkeys exposed for 1 year had smaller internal diameters and thicker walls. Following a 3-month postexposure period, static lung compliance tended to decrease in both exposed and control monkeys, but the decrease in exposed monkeys was significantly greater than that in control monkeys. No other significant differences were measured following the 3-month recovery period, although values for O_3-exposed animals remained substantially different from those for control animals. Wegner (1982) interpreted these differences as an indication that full recovery was not complete.

Morphological alterations in both rats and monkeys tend to decrease in magnitude with increasing duration of exposure to O_3, but significant alterations in the centriacinar region have still been reported at the end of long-term exposures of rats (Boorman et al., 1980; Moore and Schwartz, 1981; Barry et al., 1983; Crapo et al., 1984), monkeys (Eustis et al., 1981; Fujinaka et al., 1985), and dogs (Freeman et al., 1973). While repair, as indicated by DNA synthesis by repair cells, starts as early as 18 hours of exposure (Castleman et al., 1980; Evans et al., 1976a,b,c; Lum et al., 1978), damage continues throughout long-term exposures, but at a lower rate.

Morphological damage reported in the centriacinar region of rats and monkeys exposed to less than 1.0 ppm O_3 for 42 to 180 days includes damage to ciliated cells and centriacinar alveolar type 1 cells; hyperplasia of nonciliated bronchiolar and alveolar type 2 cells, with extension of nonciliated bronchiolar cells into more distal structures than in unexposed controls; accumulation of intraluminal and intramural inflammatory cells; and in rats, but not reported in monkeys, thickening of interalveolar septa (Boorman et al., 1980; Moore and Schwartz, 1981; Eustis et al., 1981; Barry et al., 1983; Crapo et al., 1984). Lungs from the bonnet monkeys studied by Wegner (1982) were evaluated morphologically and morphometrically by Fujinaka et al. (1985). At the end of the 1-year exposure to 0.64 ppm O_3 for 8 hr/day, a significant increase was found in the total volume of respiratory bronchioles in the lung, but their lumens were smaller in diameter because of thickened epithelium and other wall components. The reduction in diameter of the first generation respiratory bronchioles correlates with the results of the pulmonary function tests performed by Wegner (1982). Cuboidal bronchiolar epithelial cells in respiratory bronchioles were hyperplastic. Walls of respiratory bronchioles contained significantly more macrophages, lymphocytes, plasma cells, and neutrophils. Neither the numbers of fibroblasts nor amount of stainable collagen was increased significantly, but there was more amorphous intercellular material. There was also a significant increase in arteriolar media and intima.

Lung collagen content was increased after short-term exposures to O_3 concentrations ranging from 0.5 to 1.0 ppm O_3 (Last et al., 1979). This change continued during long-term exposure (Last and Greenberg, 1980; Last et al., 1984b). Exposure to 0.96 ppm O_3 resulted in increased lung collagen content in both weanling and adult rats exposed for 6 and 13 weeks, respectively, and in young monkeys exposed to 0.64 ppm O_3 for 1 year (Last et al., 1984b). Some of the weanling rats and their controls were examined after a 6-week post-exposure period in clean air following the 6-week exposure to O_3. During this post-exposure period, the differences in lung collagen content between exposed and pair-fed controls increased rather than decreased. Thus, with respect to this biochemical alteration, the post-exposure period was one of continued damage rather than recovery.

Continuation of the centriacinar inflammatory process during long-term O_3 exposures is especially important, as it appears to be correlated with remodeling of the centriacinar airways (Boorman et al., 1980; Moore and Schwartz, 1981; Fujinaka et al., 1985). There is morphometric (Fujinaka et al., 1985), morphologic (Freeman et al., 1973), and functional evidence (Costa et al., 1983; Wegner, 1982) of distal airway narrowing. Continuation of the inflammation also appears to be correlated with the increased lung collagen content (Last et al., 1979; Boorman et al., 1980; Moore and Schwartz, 1981; Last et al., 1984b) that morphologically appears predominantly in centriacinar regions of the lung.

The distal airway changes described in the above studies of ozone-exposed animals have many similarities to those reported in lungs from cigarette smokers (Niewoehner et al., 1974; Cosio et al., 1980; Hale et al., 1980; Wright et al., 1983). Even though cigarette smoking has been linked with emphysema in humans, however, there is no evidence of emphysema in the lungs of animals exposed to O_3. The previous criteria document for O_3 (U.S. Environmental Protection Agency, 1978) cited three studies reporting emphysema in laboratory animals after exposure to O_3 concentrations ranging from 0.4 to 0.88 ppm for prolonged periods (P'an et al., 1972; Freeman et al., 1974; Stephens et al., 1976); but a reevaluation of these findings based on the currently accepted definition of emphysema does not find any evidence for such claims (see Chapter 9; Section 3.1.4.2). Since then, no similar exposures (i.e., same species, O_3 concentration, and times) have been documented to confirm observations of emphysematous changes in the lungs of animals exposed to O_3.

12.3.7 Resistance to Infection

Normally the mammalian respiratory system is protected from bacterial and viral infections by the integrated activity of the mucociliary, phagocytic, and immunological defense systems. Animal models and isolated cells have been used to assess the effects of oxidants on the various components of these lung defenses and to measure the ability of these systems to function as an integrated unit in resistance against pulmonary infections. In these studies, short-term (3 hr) exposure to O_3 at concentrations of 0.08 to 0.10 ppm can increase the incidence of mortality from bacterial pneumonia (Coffin et al., 1967; Ehrlich et al., 1977; Miller et al., 1978a). Subchronic exposure to 0.1 ppm caused similar effects (Aranyi et al., 1983). Following short-term exposures to O_3, a number of alterations in lung defenses have been shown, such as (1) impairment in the ability of the lung to inactivate bacteria and viruses (Coffin et al., 1968; Coffin and Gardner, 1972; Goldstein et al., 1977; Ehrlich et al., 1979); (2) reduced effectiveness of mucociliary clearance (Phalen et al., 1980; Frager et al., 1979; Kenoyer et al., 1981; Abraham et al., 1980); (3) immunosuppression (Campbell and Hilsenroth, 1976; Aranyi et al., 1983; Thomas et al., 1981b; Fujimaki et al., 1984); (4) significant reduction in number of pulmonary defense cells (Coffin et al., 1968; Alpert et al., 1971); and (5) impaired macrophage phagocytic activity, less mobility, more fragility and membrane alterations, and reduced lysosomal enzymatic activity (Dowell et al., 1970; Hurst et al., 1970; Hurst and Coffin, 1971; Goldstein et al., 1971a,b, 1977; Hadley et al., 1977; McAllen et al., 1981; Witz et al., 1983; Amoruso et al., 1981). Such effects on pulmonary host defense have been reported in a variety of species of animals following either short-term or subchronic exposure to O_3 in combination with other airborne chemicals (Gardner et al., 1977; Aranyi et al., 1983; Ehrlich, 1980, 1983; Grose et al., 1980, 1982; Phalen et al., 1980; Goldstein et al., 1974). Studies have also indicated that the activity level of the test subject is an important variable that can influence the determination of the lowest effective concentration of the pollutant (Illing et al., 1980).

The major problem remaining is the assessment of the relevance of these animal data to humans. If animal models are to be used to reflect the toxicological response occurring in humans, then the end point for comparison of such studies should be morbidity rather than mortality. A better comparison in humans would be the increased prevalence of respiratory illness in the community. Such a comparison is proper since both mortality (animals) and morbidity (humans) result from an impairment in pulmonary defenses. Ideally, studies of pulmonary host defenses should be performed in man using epidemiological or volunteer methods of study. Unfortunately, such studies have not yet been reported. Therefore, attention must be paid to experiments conducted with animals.

Present knowledge of the physiology, metabolism, and function of host defense systems has come primarily from various animal systems, but it is generally accepted that the basic host defence mechanisms are similar in animals and man. Green (1984) recently delineated the many similarities that exist between the rodent and human antibacterial defenses. Both defenses consist of the same defense components, which together act to maintain the lung free of bacteria. The effects seen in animals represent alterations in basic biological systems. An equivalent response (e.g., mortality) may not be expected in man, but similar alterations in basic defense mechanisms could occur in humans because they possess pulmonary defense systems equivalent to those in laboratory animals. It is understood that different exposure levels may be required to produce similar responses in humans. The concentrations of O_3 at which effects become evident can be influenced by a number of factors, such as preexisting disease, dietary factors, combinations with other pollutants, and the presence of other environmental stresses. Although not confirmed by experimental data, it is possible that humans exposed to O_3 could experience decrements in host defenses; but at the present time, the exact concentration at which effects might occur in man cannot be predicted, nor can the severity of the effect.

12.3.8 Extrapulmonary Effects of Ozone

Because of the high degree of reactivity of O_3 with biological tissue, it is not clear whether O_3 reaches the circulation. Results from mathematical modeling (Miller et al., 1985) suggest that only a small fraction of O_3 can penetrate the air-blood barrier. Several studies discussed in Chapters 9 and

10 are indicative, however, of either direct or indirect extrapulmonary effects of ozone exposure. For example, alterations in red blood cell morphology and enzymatic activity, as well as cytogenetic effects in circulating lymphocytes, have been reported in man and laboratory animals. Other organ systems of the body may also be involved. Exposure to O_3 may have central nervous system effects, since subjective limitations in performance of vigilance tasks have been observed in man and laboratory animals. Cardiovascular, reproductive, and teratological effects of O_3 have also been reported in laboratory animals, along with changes in endocrine function; but the implications of these findings for human health are difficult to judge. More recent studies in laboratory animals have shown that hepatic metabolism of xenobiotic compounds may be impaired by O_3 inhalation. While some of these systemic effects, such as decrements in exercise and vigilance performance, may be attributed to odor perception or respiratory irritation, the reasons for the others are more difficult to conceptualize. These effects may result from direct contact with O_3 or, more likely, from contact with a reactive product of O_3 that penetrates to the blood and is transported to the other organs.

Cytogenetic and mutational effects of ozone are controversial. In human cells in culture, a significant increase in the frequency of sister chromatid exchanges has been reported to occur after exposure to concentrations of ozone as low as 0.25 ppm for 1 hr (Guerrero et al., 1979). Lymphocytes isolated from animals were found to have significant increases in the numbers of chromosome (Zelac et al., 1971a,b) and chromatid (Tice et al., 1978) aberrations, after 4- to 5-hr exposures to 0.2 and 0.43 ppm ozone, respectively. Single-strand breaks in DNA of mouse peritoneal exudate cells were measurable after a 24-hr exposure to 1 ppm ozone (Chaney, 1981). Gooch et al. (1976) analyzed the bone marrow samples from Chinese hamsters exposed to 0.23 ppm of O_3 for 5 hr and the leukocytes and spermatocytes from mice exposed for up to 2 weeks to 0.21 ppm of O_3. No effect was found on either the frequency of chromatid or chromosome aberrations, nor were there any reciprocal translocations in the primary spermatocytes. Small increases observed in chromatid lesions in peripheral blood lymphocytes from humans exposed to 0.5 ppm ozone for 6 or 10 hr were not significant because of the small number (n=6) of subjects studied (Merz et al., 1975). Subsequent investigations, however, with more human subjects exposed to ozone at various concentrations and for various times have failed to show any cytogenetic effect considered to be the result of ozone exposure (McKenzie et al., 1977; McKenzie, 1982; Guerrero et al., 1979). In addition, epidemiological studies have not shown any evidence of chromosome changes in peripheral lymphocytes of humans exposed to ozone in the ambient environment (Scott and Burkart, 1978; Magie et al., 1982). Clearly, additional evaluation of potential chromosomal effects in humans exposed to O_3 is needed. Evidence now available, however, fails to demonstrate any cytogenetic or mutagenic effects of ozone in humans when exposure schedules are used that are representative of exposures that the population at large might actually experience.

With the exception of peripheral blood lymphocytes, the potential genotoxic effects of ozone for all of the other body tissues are unknown. No cytogenetic investigations have been conducted on the respiratory tissues of animals exposed to ozone, even though these tissues are exposed to the highest concentrations and are also the target of most of the toxic manifestations of ozone. Clearly, ozone-induced genotoxicity data from peripheral blood lymphocytes cannot be extrapolated to other organs, such as the lungs or reproductive organs.

Ozone exposure produces a number of hematological and serum chemistry changes both in rodents and man, but the physiological significance of these effects is unknown. Most of the hematological changes appeared to be linked to a decrease in RBC GSH content (Menzel et al., 1975; Buckley et al., 1975; Posin et al., 1979; Linn et al., 1978) at concentrations of 0.2 ppm for 30 to 60 min in man, or 0.5 ppm for 2.75 hr in sheep, or 0.5 ppm continuously for 5 days in mice and rats. Heinz bodies, disulfide cross-linked methemoglobin complexes attached to the inner RBC membrane, were detected in mice exposed to ozone (Menzel et al., 1975). Inhibition of RBC acetylcholinesterase was found in mouse (Goldstein et al., 1968), human (Buckley et al., 1975), and squirrel monkey RBCs (Clark et al., 1978) at concentrations of 0.4 to 0.75 ppm and times as short as 2.75 hr in man or 4 hr/day for 4 days in monkeys. Loss of RBC acetylcholinesterase could either be mediated by membrane peroxidation or by loss of acetylcholinesterase thiol groups at the active site. Dorsey et al. (1983) observed that the deformability of CD-1 mouse RBCs decreased on exposure to 0.7 and 1 ppm for 4 hr. Deformability also decreased at 0.3 ppm, but was not statistically significant. These data support the concept of membrane damage to circulating RBCs, which appears to be similar in most species of animals studied and in normal human RBCs exposed to O_3.

12.4 HEALTH EFFECTS IN INDIVIDUALS WITH PREEXISTING DISEASE

12.4.1 Patients with Chronic Obstructive Lung Disease (COLD)

Patients with mild COLD have not shown increased responsiveness to O_3 in controlled human exposure studies. For example, Linn et al. (1982a, 1983b) and Hackney et al. (1983) showed no changes in symptoms or lung function at 0.12, 0.18, or 0.25 ppm O_3 (1 hr with intermittent light exercise). Likewise, Solic et al. (1982) and Kehrl et al. (1983, 1985) found no significant changes in symptoms or function at 0.2 or 0.3 ppm O_3 (2 hr with intermittent moderate exercise). At higher concentrations, however, Kulle et al. (1984) found decreased lung function in a group of 20 smoking chronic bronchitics at 0.4 ppm (3 hr with intermittent moderate exercise) on day 1 of exposure and upon reexposure at day 9 (fourth day following cessation of repeated daily exposures); these subjects were less responsive to O_3 than healthy nonsmokers.

There is suggestive evidence that bronchial reactivity is increased in some subjects with COLD (two of three) following exposure to 0.1 ppm O_3 (König et al., 1980). Small decreases in arterial O_2 saturation (S_aO_2) have also been observed in COLD subjects exercising at 0.12 ppm O_3 for 1 hr (Linn et al., 1982a; Hackney et al., 1983) and at 0.2 ppm O_3 for 2 hr (Solic et al., 1982). Decreased SaO_2 was also seen at higher O_3 concentrations but was not significant (Linn et al., 1983b; Kehrl et al., 1985). Interpretation of small differences in S_aO_2 or their physiological and clinical significance is therefore uncertain. In addition, since many of the COLD subjects were smokers, the interpretation of small changes in S_aO_2 is complicated. Further studies are needed to resolve this issue, particularly on COLD subjects exposed to O_3 at higher exercise levels.

One difficulty in attempting to characterize the responsiveness of patients with COLD is that they exhibit a wide diversity of clinical and functional states. These range from a history of smoking, cough, and minimal functional impairment to chronic disability that is usually combined with severe changes in blood gases or respiratory mechanical behavior. The chief locus of damage may also vary: either the bronchi (chronic bronchitis) or parenchyma (emphysema) may dominate the clinical picture. Finally, the mixture of acute and chronic inflammatory processes may vary considerably among patients. Even with strict selection criteria, however, it may be very difficult to sort out many of these manifestations of COLD in the design of pollutant-exposure studies.

12.4.2 Asthmatics

There is as yet no definitive laboratory evidence demonstrating that mild asthmatics are functionally more responsive than healthy individuals to O_3. Linn et al. (1978) found no significant changes in lung function, as indicated by forced expiratory spirometry or the nitrogen washout test, when a heterogeneous group of adult asthmatics with mild to moderate bronchial obstruction was exposed to 0.20 ppm O_3 for 2 hr with intermittent light exercise; increased symptom scores were noted, however. Silverman (1979) found minimal changes in forced expiratory spirometry following 2-hr exposures of adult asthmatics to 0.25 ppm O_3 while at rest. Although group mean changes were not statistically significant, one third of the subjects who rested for 2 hr while inhaling 0.25 ppm O_3 demonstrated a greater than 10 percent decrement in lung function. Changes of this magnitude have not been reported in normal subjects under these conditions. In laboratory field studies with ambient air containing an average concentration of 0.17 ppm O_3, Linn et al. (1980) found small but statistically significant decrements in forced expiratory measures in both healthy and asthmatic adults, following 2-hr exposures with intermittent light exercise. The magnitude of functional responses did not differ statistically between the two groups. Finally, Koenig et al. (1985) found no significant changes in pulmonary function or symptoms when a group of adolescent subjects with atopic, extrinsic asthma were exposed at rest to 0.12 ppm O_3 for 1 hr.

The studies reported above are not considered definitive since major limitations leave open the question of whether the pulmonary function of asthmatics is more affected by O_3 than that of healthy subjects. Intake of medication was not controlled in several of the studies, and some subjects continued to use oral medication during testing. Adequate characterization of subjects is lacking in most studies and, as a result, group mean changes could not be detected because of the large variability in responses from such heterogeneous groups. For example, some of the subjects in one study (Linn et al., 1978) showed evidence of chronic obstructive lung disease in addition to asthma. Most of the normal subjects (70 percent) in the Linn et al. (1980) study, in which asthmatics were compared to normals, had a history of allergy and appeared atypically reactive to the O_3 exposure. In addition, the subjects in these studies either performed light exercise or rested while exposed. In view of the recognized importance of minute ventilation, which increases proportionately with the intensity of exercise, in determining the response to O_3, additional testing at higher levels of exercise should be undertaken.

The specific measurements of pulmonary function and the exposure protocols employed in the above studies may be inappropriate for ascertaining pulmonary effects in asthmatic subjects. Asthma is essentially characterized by bronchoconstriction. Compared to airway resistance, some measures of forced expiratory spirometry are less sensitive to bronchoconstriction, since fairly severe bronchoconstriction must occur in order to affect decrements in these measures. McDonnell et al. (1983), reporting on healthy subjects exposed to levels of O_3 as low as 0.12 ppm with heavy intermittent exercise, attributed small (<5 percent) decrements in forced expiratory spirometry to a reduced inspiratory capacity resulting from stimulation or sensitization of airway receptors by O_3 (see Section 12.3.5). They also observed that there was no correlation between changes in airway resistance and forced expiratory spirometry for individual subjects, which prompted them to postulate two different mechanisms of action. It may be that the sensitivity of the mechanism affecting inspiratory capacity is the same in asthmatics and normals, while the mechanism affecting airway resistance is different.

Epidemiological findings provide only qualitative evidence of exacerbation of asthma at ambient concentrations of O_3 below those generally associated with symptoms or functional changes in healthy adults. Whittemore and Korn (1980) and Holguin et al. (1985) found small increases in the probability of asthma attacks associated with previous attacks, decreased temperature, and incremental increases in oxidant and O_3 concentrations, respectively. Lebowitz et al. (1982, 1983, 1985) and Lebowitz (1984) also showed effects in asthmatics, such as decreased peak expiratory flow and increased respiratory symptoms, that were related to the interaction of O_3 and temperature. All of these studies have questionable effects from other pollutants, particularly inhalable particles. The major problem in epidemiological studies, therefore, has been the lack of definitive information on the effects of O_3 alone, since there is confounding by the presence of other environmental conditions in ambient air. Other factors leading to inconsistencies between epidemiological and controlled-laboratory studies include (1) differences in the pulmonary function tests employed, (2) differences in study subjects, since the general population contains individuals with more severe disease than can be studied in controlled human exposures, (3) insufficient clinical information in most of these studies, or (4) the lack of data on other, unmeasured pollutants and environmental conditions in ambient air.

12.4.3 Subjects with Allergy, Atopy, and Ozone-Induced Hyperreactivity

Allergic or hypersensitivity disorders may be recognized by generalized systemic reactions as well as localized reactions in various sites of the body. The reactions can be acute, subacute, or chronic; immediate or delayed; and may be caused by a variety of physical and chemical stimuli (antigens). Although many hypersensitive individuals in the population have a family history of allergy, a true allergic reaction is one that is classically elicited through an immunological mechanism (i.e., antigen-antibody response), thereby distinguishing allergic responses from simple chemical or pharmacologic reactions. There are also some individuals with family histories who develop natural or spontaneous allergies, defined generally as atopy. Determination of the specific allergens (antigens) responsible for these disorders is often difficult, but clinical history, physical examination, skin tests, and selective diets are very useful. A more definitive evaluation can be provided by pulmonary function tests (e.g., airway reactivity), serum IgE levels, and nasal cytology. The information available on the responsiveness of these individuals to ozone, i.e., whether they differ from normal non-allergic, non-atopic individuals, is sparse.

Hackney et al. (1977a) found decreases in spirometric function among atopic individuals exposed to 0.5 ppm O_3 with light intermittent exercise. Neither Folinsbee et al. (1978), in a controlled laboratory exposure, nor Linn et al. (1980), in a field study in the Los Angeles area, distinguished between the responses of normal subjects and allergic non-asthmatic subjects. In the latter study, spirometric function was reduced and symptoms were increased in association with an average ambient O_3 concentration of 0.17 ppm. Similarly, Lebowitz et al. (1982, 1983) reported, after adjusting for other covariables, that O_3 and TSP were independently associated with peak flow in adults with airway obstructive disease.

Some healthy subjects with no prior history of respiratory symptoms or allergy demonstrate increased nonspecific airway sensitivity resulting from O_3 exposure (Golden et al., 1978; Holtzman et al., 1979; König et al., 1980; Dimeo et al., 1981; Kulle et al., 1982b). Airway responsiveness is typically defined by changes in specific airway resistance produced by a provocative bronchial challenge to drugs like acetylcholine, methacholine, or histamine, administered after O_3 exposure. In one study (Holtzman et al., 1979), in which subjects were classified as atopic or nonatopic based on medical history and allergen skin testing, the induction and time course of increased bronchial reactivity after exposure to O_3 were unrelated to the presence of atopy. An association of O_3-induced increases in airway responsiveness with airway inflammation has been reported in dogs at high O_3 concentrations (1 to 3 ppm) (Holtzman et al., 1983a,b; Fabbri et al., 1984); and in sheep at 0.5 ppm O_3 (Sielczak et al., 1983). Little is known, however, about this relationship in animals at lower O_3 concentrations (<0.5 ppm), and the possible association between O_3-induced inflammation and airway hyperresponsiveness in human subjects has not been explored systematically.

12.5 EXTRAPOLATION OF EFFECTS OBSERVED IN ANIMALS TO HUMAN POPULATIONS

12.5.1 Species Comparisons

Comparisons of the effects of ozone on different animal species are of value in attempting to understand whether man might experience similar effects. Two criteria are useful for judging whether effects seen in animals may plausibly be expected to occur in man: (1) the same effects occur in multiple animal species; and (2) the mechanisms of toxicity underlying the observed effects are common across animal species and between animals and man. Thus, if only one of several tested species experienced a given effect of ozone, this effect might be species-specific and might not occur in man. Conversely, if several animal species, with all their inherent differences, shared a given effect of ozone, it would be reasonable to infer that all mammalian species, including man, would be susceptible to that effect from ozone. A commonality of effects across species would be expected, provided the effects were related to mechanisms that are shared across species. In the case of ozone, the proposed major molecular mechanisms of action are the oxidation of polyunsaturated fatty acids and the oxidation of thiols or amino acids in tissue proteins or lower-molecular-weight peptides. Since the affected molecules are identical across all species, then any differences in the observed responses between species would be a function of species differences in other factors, such as delivered doses or subsequent processes of injury and repair. For example, a likely target site for O_3 toxicity is the cellular membrane, such as the membrane of cells like the Type 1 and ciliated cells that cover a large surface area of the respiratory tract. Since there are no major interspecies differences in cell membranes, and membranes are composed of proteins and lipids, then both proposed molecular mechanisms of O_3 toxicity could occur at the cellular membrane. In fact, the two proposed mechanisms most likely occur simultaneously. Although the mechanisms of toxicity would be common across species, the consequent toxic impact on the membrane, the cell, and surrounding tissue would be influenced by species-specific differences, such as antioxidant defenses or repair mechanisms. Even if both criteria cited above are met, it does not imply that the concentrations at which man might experience the observed effects are the same as those eliciting the effects in experimental animals.

The health data base for ozone includes hundreds of studies in about eight species, and even more strains, of laboratory animals. Generally, for a given effect, whether it be on lung morphology, physiology, biochemistry, or host defenses, all species tested have been responsive to ozone, albeit sometimes at different concentrations. The few studies of several species having at least two points of identity for comparison will be discussed.

Morphological examinations of the lungs of several species have been conducted after ozone exposure. In the groups studied, there are significant differences in lung structure. Man, nonhuman primates, and dogs have both nonrespiratory and respiratory bronchioles, while respiratory bronchioles are either absent or poorly developed in mice, rats, and guinea pigs. Additional differences exist. Nonetheless, a characteristic ozone lesion occurs at the junction of the conducting airways and the gaseous exchange tissues, regardless of species differences in structure. The typical effect in all the species examined is damage to ciliated and Type 1 cells and hyperplasia of nonciliated bronchiolar cells and Type 2 cells. An increase in inflammatory cells is also observed. Such changes have been observed after a 7-day intermittent exposure of monkeys to 0.2 ppm (Dungworth et al., 1975; Castleman et al., 1977) and of rats to 0.2 ppm (Schwartz et al., 1976). With different exposure regimens, similar effects occur in cats (0.26 ppm, endotracheal tube, about 6 hr, Boatman et al., 1974), mice (0.5 ppm, 35 days, Zitnik et al., 1978), and guinea pigs (0.5 ppm, 6 mo, Cavender et al., 1978). For these studies, lower concentrations of ozone were not tested. Unfortunately, quantitative comparisons between monkey and rat studies is not possible because of inadequate data. Nonetheless, responses were roughly equivalent under similar exposure conditions in these two species, even though major structural differences exist between them.

Pulmonary function of eight species of animals has been studied after exposure to ozone. Short-term exposure for 2 hr to O_3 concentrations as low as 0.22 ppm produces rapid, shallow breathing. Similar changes in respiration have been observed in man during exposure to comparable ozone concentrations, as shown in Table 12-4. The onset of these effects is rapid and appears to be related to the ozone concentration. In a literature review, Mauderly (1984) compared changes in breathing patterns of humans and guinea pigs during and after a 2-hr exposure to 0.7 ppm O_3. The respiratory frequency increased and tidal volume decreased, with similar patterns in these two species during exposure, and returned toward normal in the first 3 hr after exposure.

Enhanced airway reactivity to inhaled bronchoconstrictive agents has also been observed in animals and man after O_3 exposure (Table 12-5). Short-term exposure to O_3 concentrations as low as 0.32 ppm increases airway responsiveness to provocative aerosols such as acetylcholine, carbachol, methacholine, or histamine in sheep, dogs, and humans. However, the time course of this response may be species-specific. A maximum response is obtained immediately after exposure in man but appears to be delayed by 24 hr in sheep and dogs.

Mauderly (1984) has also compared the effect of 2-hr O_3 exposures on airway constriction in humans, guinea pigs, and cats. Although measured indices of airflow limitation are similarly depressed in both animals and man, there are too many differences in the experimental methods and too few species studied to provide an adequate comparison.

Qualitative comparisons of changes in breathing patterns and airway reactivity indicate that many similarities occur during exposure of animals and humans to ozone. However, quantitative extrapolation of these effects may be limited by the small number of studies having similar experimental procedures and similar exposure levels. Other effects of short- and long-term ozone exposure on lung function have been observed (Chapter 9), but there are insufficient points of identity in the experiments to permit direct comparisons among animal species or between animals and man.

Species comparisons of host defense against infection are theoretically possible, given the abundance of information describing the effect of exposure to photochemical oxidants in mice and other rodents (see Section 12.3.7). Therefore, examination of the similarities between host antibacterial defense systems in rodents and man are in order. Green (1984) has delineated the similarities as follows. Both defense systems consist of an aerodynamic

TABLE 12-4. COMPARISON OF THE ACUTE EFFECTS OF OZONE ON BREATHING PATTERNS IN ANIMALS AND MAN

Ozone[a] concentration µg/m³	Ozone[a] concentration ppm	Measurement[b] method	Exposure duration	Activity[c] level ($\dot{V}_E$)	Observed effects(s)	Species	Reference
392 686	0.20 0.35	UV	1 hr (mouthpiece)	CE(77.5)	Increased f_R and decreased V_T.	Human	Adams and Schelegle, 1983
431 804 1568	0.22 0.41 0.8	CHEM	2 hr	R	Concentration-dependent increase in f_R for all exposure levels.	Guinea pig	Amdur et al., 1978
470 588 784	0.24 0.30 0.40	CHEM	2.5 hr	IE(65)	Increased f_R and decreased V_T.	Human	McDonnell et al., 1983
588	0.3	MAST	1 hr (mouthpiece)	CE(34.7, 51)	Increased f_R and decreased V_T.	Human	DeLucia et al., 1983
588	0.3	UV	1 hr (mouthpiece)	CE(66)	Increased f_R and decreased V_T.	Human	DeLucia and Adams, 1977
588	0.3	UV	1 hr	CE(55)	Increased f_R and decreased V_T.	Human	Gibbons and Adams, 1984
588 980	0.3 0.5	CHEM	2 hr	IE(31,50,67)	Increased f_R and decreased V_T with time of exposure; significant linear correlations with O_3.	Human	Folinsbee et al., 1978
666 1333 2117 2646	0.34 0.68 1.08 1.35	NBKI	2 hr	R	Increased f_R and decreased V_T during exposure to all O_3 concentrations.	Guinea pig	Murphy et al., 1964
725 980 1470	0.37 0.50 0.75	MAST	2 hr	IE(29)	Dose-dependent increase in f_R and decrease in V_T.	Human	Folinsbee et al., 1975
980	0.5	NBKI	2 hr	R	Increased f_R.	Guinea pig	Yokoyama, 1969
1100	0.56	CHEM	2 hr	R	Abnormal, rapid, shallow breathing while exercising on a treadmill after exposure.	Dog	Lee et al., 1979
1470	0.75	MAST	2 hr	IE	Increased f_R and decreased V_T at maximum workloads only.	Human	Folinsbee et al., 1977a

[a] Ranked by lowest observed effect level.

[b] Measurement method: MAST = KI-Coulometric (Mast meter); CHEM = gas phase chemiluminescence; UV = ultraviolet photometry; NBKI = neutral buffered potassium iodide.

[c] Minute ventilation reported in L/min or as a multiple of resting ventilation. R = rest; IE = intermittent exercise; CE = continuous exercise.

TABLE 12-5. COMPARISON OF THE ACUTE EFFECTS OF OZONE ON AIRWAY REACTIVITY IN ANIMALS AND MAN

Ozone[a] concentration µg/m³	Ozone[a] concentration ppm	Measurement[b] method	Exposure duration	Activity[c] level (V_E)	Observed effects(s)	Species	Reference
627	0.32	MAST	2 hr	R	SR_{aw} increased with ACh challenge.	Human	König et al., 1980
784	0.4	CHEM	3 hr	IE(4-5xR)	SG_{aw} decreased with methacholine; attenuation develops with repeated exposures.	Human	Kulle et al., 1982b
784	0.4	UV	2 hr	IE(2xR)	SR_{aw} increased with histamine challenge; attenuation develops with repeated exposure. No effect on bronchial reactivity at 0.2 ppm.	Human	Dimeo et al., 1981
980	0.5	CHEM	2 hr	R	R_L increased with carbachol 24 hr but not immediately after exposure.	Sheep	Abraham et al., 1980
1176	0.6	UV	2 hr	IE(2xR)	SR_{aw} increased with histamine and methacholine in atopic and non-atopic subjects.	Human	Holtzman et al., 1979
1176	0.6	CHEM	2 hr	R	Bronchoreactivity to histamine; may persist for up to 3 weeks.	Human	Golden et al., 1978
1372	0.7	CHEM	2 hr	R	R_L increased with histamine 24 hr but not 1 hr after O_3 exposure.	Dog	Lee et al., 1977
1960	1.0	UV	2 hr	R	R_L increased with ACh and histamine 1 hr and 24 hr after exposure.	Dog	Holtzman et al., 1983a,b

[a] Ranked by lowest observed effect level.

[b] Measurement method: MAST = KI-Coulometric (Mast meter); CHEM = gas phase chemiluminescence; UV = ultraviolet photometry.

[c] Minute ventilation reported in L/min or as a multiple of resting ventilation. R = rest; IE = intermittent exercise.

filtration system; a fluid lining layer covering the respiratory membranes; an active transport mechanism for removal and inactivation of viable microorganisms; pulmonary cells (alveolar macrophages, polymorphonuclear leukocytes); and immune secretions of lymphocytes and plasma cells. These similarities provide an ideal basis for qualitative extrapolation, since in man and rodents these components act in concert to maintain the lung free of bacteria. On the basis of O_3 exposure data and the similarities in host antibacterial defense systems, Goldstein (1984) has drawn the following conclusions. First, sufficient similarity exists between the major defense mechanisms in rodents and humans to permit the use of the rat as a human surrogate. Second, the pulmonary antibacterial system is a sensitive means of assessing potential toxicity of oxidants. Third, pollutant-induced abnormalities in the individual components of the host defense system permit bacterial proliferation and disease. Fourth, results can be qualitatively extrapolated from rodents to humans. Although quantitative relationships may also exist, the detailed information is not yet available for such extrapolation. Too few studies of antiviral host defenses after O_3 exposure exist to form any accurate conclusions regarding viral infections.

Rats and monkeys have been examined for changes in lung biochemistry following ozone exposure. In these animals exposed for 7 days (8 hr/day) to 0.8 ppm ozone (DeLucia et al., 1975), glucose-6-phosphate dehydrogenase activity was elevated to a roughly equivalent degree. Glutathione reductase activity was increased in rats, but not monkeys. Chow et al. (1975) also compared these species after exposure to 0.5 ppm ozone for 8 hr/day for 7 days. Antioxidant enzymes were increased in the rats, but not in the monkeys. The authors referred to "relatively large variations" in the monkey data. Oxygen consumption was measured in rats and monkeys after a 7-day (8 hr/day) exposure to several levels of ozone (Mustafa and Lee, 1976). Rhesus monkeys may have been slightly less responsive than rats. However, at 0.5 ppm ozone, bonnet monkeys and rats had roughly equivalent increases. In all of these reports, there was no mention of statistical comparisons between species or of power calculations that would indicate whether, under the experimental conditions of data variability, there was equivalent power for statistically detecting effects in both species. In a few of the reports, the number of animals was not given. Mustafa et al. (1982) compared mice to three strains of rats exposed to 0.45 ppm ozone continuously for 5 days. Antioxidant metabolism and oxygen consumption were measured. Generally, increases in enzyme activities were observed in both species; in several cases the increase in the mice was statistically greater than the increase in the rats.

For extrapulmonary effects, the only species comparison was made by Graham et al. (1981). Female mice, rats, and hamsters had an increase in pentobarbital-induced sleeping time after a 5-hour exposure to 1 ppm ozone. Under the experimental conditions used, relative species responsivity cannot be assessed.

An analysis of the animal toxicological data for ozone indicates that the rat is the species most often tested. Other species often used include mice, rabbits, guinea pigs, and monkeys. A few dog, cat, sheep, and hamster studies exist. As has been noted above, very few species comparisons can be made because of differences in exposure regimens and measurement techniques. Even when direct comparisons are possible, interpretation is difficult. Statements regarding responsiveness can be made, but statements about sensitivity (e.g., responses to an equivalent delivered dose) cannot be made until more dosimetry and other types of data are available. Nonetheless, even with the wide variation in techniques and experimental designs, acute and subchronic exposures to levels of ozone less than 0.5 ppm produce remarkably similar types of responses in many species of animals. Thus, it may be hypothesized that man experiences more types of effects from exposure to ozone than can be deduced from human studies. Types of effects for which substantial animal data bases exist include changes in lung structure, biochemistry, and host defenses. However, the risks to man from breathing ambient levels of ozone cannot fully be determined until quantitative extrapolations of animal results can be made.

12.5.2 Dosimetry Modeling

Dosimetry refers to determination of the amount of ozone that reaches specific sites in animals and man, while sensitivity relates to the likelihood of equivalency of biological response given the delivery of the same dose of ozone to a target site in different species. A coupling of these two elements is required to permit quantitative interspecies comparisons of toxicological results from different experiments.

Although additional research is needed on dosimetry and on species sensitivity before quantitative extrapolations can confidently be made between species, only dosimetry is sufficiently advanced for discussion here. Because the factors affecting the transport and absorption of O_3 are general to animals and man, dosimetry models can be formulated that use appropriate species anatomical and ventilatory parameters to describe O_3 absorption. Thus far, theoretical modeling efforts (McJilton et al., 1972; Miller et al., 1978b, 1985) have focused on the lower respiratory tract.

Largely because of the technical ease of measuring ozone uptake in the head, nasopharyngeal removal of ozone has been experimentally studied in the dog (Vaughan et al., 1969; Yokoyama and Frank, 1972; Moorman et al., 1973), rabbit (Miller et al., 1979), and guinea pig (Miller et al., 1979). To date, information on nasopharyngeal removal of O_3 in man is not available. Since nasopharyngeal removal of O_3 serves to lessen the insult to lower respiratory tract tissue, an assessment of species differences in this area is critical to interspecies comparisons of dosimetry.

Damage to all respiratory tract regions occurs in animals exposed to O_3, with location and intensity dependent upon concentration and exposure duration. When comparisons are made at the analogous anatomical sites, the morphological effects of O_3 on the lungs of a number of animal species are remarkably similar. Despite inherent differences in the anatomy of the respiratory tract between various experimental animals and man, the junction between the conducting airways and the gas exchange region is the site most severely damaged by O_3 exposure in animals (see Section 9.3.1). This finding is consistent with the inference that this region is also most likely the principal site affected in man. Dosimetry model simulations (Miller et al., 1978b) predict that the maximal tissue dose occurs at the region of predominant morphological damage in animals. The overall similarity of the predicted O_3 dose patterns in animal lungs studied thus far (rabbits and guinea pigs) extends to the simulation of O_3 uptake in humans (Miller et al., 1985) (see Section 9.2.3.1).

The consistency and similarity of the human and animal lower respiratory tract dose curves lend strong support to the feasibility of extrapolating to man the results obtained from animals exposed to O_3. In the past, extrapolations have usually been qualitative in nature. With additional research in areas that are basic to the formulation of dosimetry models, quantitative dosimetric differences among species can be determined. If, in addition, more information is obtained on species sensitivity to a given dose, significant advances can be made in quantitative extrapolations of effects from exposure to O_3. Since animal studies are the only available approach for investigating the full array of potential effects induced by exposure to O_3, quantitative use of animal data is in the interest of better establishing the O_3 levels to which man can safely be exposed.

12.6 HEALTH EFFECTS OF OTHER PHOTOCHEMICAL OXIDANTS AND POLLUTANT MIXTURES

Ozone is considered to be chiefly responsible for the adverse effects of photochemical air pollutants, largely because of its relative abundance compared with other photochemical oxidants. Still, the coexistence of other reactive oxidants (Section 12.2.2) suggests that the potential effects of other ambient oxidants should be examined. Animal and clinical research, however, has centered largely on O_3; very limited effort has been devoted to studies of peroxyacetyl nitrate (PAN) and hydrogen peroxide (H_2O_2). Field and epidemiological studies evaluate health effects associated with exposure to the ambient environment, making it difficult to single out the oxidant species responsible for the observed effects.

12.6.1 Effects of Peroxyacetyl Nitrate

There have been too few controlled toxicological studies with the other oxidants to permit a sound scientific evaluation of their contribution to the toxic action of photochemical oxidant mixtures. The few animal toxicology studies on PAN indicate that it is less acutely toxic than O_3. When the effects seen after exposure to O_3 and PAN are examined and compared, it is obvious that the test animals must be exposed to concentrations of PAN much greater than those needed with O_3 to produce a similar effect on lethality, behavior modification, morphology, or significant alterations in host pulmonary defense system (Campbell et al., 1967; Dungworth et al., 1969; Thomas et al., 1979, 1981a).

All of the available controlled human studies with other photochemical oxidants have been limited to a series of reports on the effects of PAN on healthy young and middle-aged males during intermittent moderate exercise (Smith, 1965; Drinkwater et al., 1974; Raven et al., 1974a,b, 1976; Gliner et al., 1975). No significant effects were observed at PAN concentrations of 0.25 to 0.30 ppm, which are higher than the daily maximum concentrations of PAN reported for relatively high oxidant areas (0.047 ppm). One study (Drechsler-Parks et al., 1984) suggested a possible simultaneous effect of PAN and O_3; however, there are not enough data to evaluate the significance of this effect.

Field and epidemiological studies have found few specific relationships between reported health effects and PAN concentrations. The increased prevalence of eye irritation reported during ambient air exposures has been associated with PAN as well as other photochemical reaction products (National Air Pollution Control Administration, 1970; Altshuller, 1977; National Research Council, 1977; U.S. Environmental Protection Agency, 1978; Okawada et al., 1979). In one of these studies (Okawada et al., 1979), eye irritation was produced experimentally in high school students at concentrations of PAN >0.05 ppm. An increased incidence of other health symptoms such as chest discomfort was reported along with eye irritation as PAN concentrations in the ambient air increased from 0 to 0.012 ppm (Javitz et al., 1983). However, the significance of these symptomatic responses is questionable since functional changes reported in this study for the subjects exposed to total oxidants (O_3 and PAN) were similar to those found for O_3 alone.

12.6.2 Effects of Hydrogen Peroxide

Toxicological studies on H_2O_2 have been performed at concentrations much higher than those reported to occur in the ambient air (see Section 12.2). The majority have been mechanistic studies using various *in vitro* techniques for exposure. Very limited information is available on the health significance of inhalation exposure to gaseous H_2O_2 in laboratory animals. No significant effects were observed in rats exposed for 7 days to >95 percent H_2O_2 gas with a concentration of 0.5 ppm in the presence of inhalable ammonium sulfate particles (Last et al., 1982). Because H_2O_2 is highly soluble, it is generally assumed that it does not penetrate into the alveolar regions of the lung but is instead deposited on the surface of the upper airways (Last et al., 1982). Unfortunately, no studies have been designed to look for possible effects in this region of the respiratory tract.

A few *in vitro* studies have reported cytotoxic, genotoxic, and biochemical effects of H_2O_2 when using isolated cells or organs (Stewart et al., 1981; Bradley et al., 1979; Bradley and Erickson, 1981; Speit et al., 1982; MacRae and Stich, 1979). Although these studies can provide useful data for studying possible mechanisms of action, it is not yet possible to extrapolate these responses to those that might occur in the mammalian system.

12.6.3 Interactions with Other Pollutants

Controlled human exposures have not consistently demonstrated any enhancement of respiratory effects for combined exposures of O_3 with SO_2, NO_2, CO, and H_2SO_4 or other particulate aerosols. Ozone alone is considered to be responsible for the observed effects of those combinations or with multiple mixtures of these pollutants. Studies reviewed in the previous O_3 criteria document (U.S. Environmental Protection Agency, 1978) suggested that mixtures of SO_2 and O_3 at a concentration of 0.37 ppm are potentially more active than would be expected from the behavior of the gases acting separately (Bates and Hazucha, 1973; Hazucha and Bates, 1975). High concentrations of inhalable aerosols, particularly H_2SO_4 or ammonium sulfate, could have been responsible for the results (Bell et al., 1977). Subsequent studies, however, of O_3 mixtures with SO_2, H_2SO_4, or ammonium sulfate have not conclusively demonstrated any interactive effects (Bedi et al., 1979, 1982; Kagawa and Tsuru, 1979c; Kleinman et al., 1981; Kulle et al., 1982a; Stacy et al., 1983).

Combined exposure studies in laboratory animals have produced varied results, depending upon the pollutant combination evaluated, the exposure design, and the measured variables. Additive or possibly synergistic effects, or both, of O_3 exposure in combination with NO_2 have been described for increased susceptibility to bacterial infection (Ehrlich et al., 1977, 1979; Ehrlich, 1980, 1983), morphological lesions (Freeman et al., 1974), and increased antioxidant metabolism (Mustafa et al., 1984). Additive or possibly synergistic effects from exposure to O_3 and H_2SO_4 have also been reported for host defense mechanisms (Gardner et al., 1977; Last and Cross, 1978; Grose et al., 1982), pulmonary sensitivity (Osebold et al., 1980), and collagen synthesis (Last et al., 1983), but not for morphology (Cavender et al., 1977; Moore and Schwartz, 1981). Mixtures of O_3 and $(NH_4)_2SO_4$ had synergistic effects on collagen synthesis and morphometry, including percentage of fibroblasts (Last et al., 1983, 1984a).

Combining O_3 with other particulate pollutants produces a variety of responses in laboratory animals, depending on the endpoint measured. Mixtures of O_3, $Fe_2(SO_4)_3$, H_2SO_4, and $(NH_4)_2SO_4$ produced the same effect on clearance rate of particles from the lung as exposure to O_3 alone (Phalen et al., 1980). However, in studies measuring changes in host defenses, the combination of O_3 with NO_2 and $ZnSO_4$ (Ehrlich, 1983) or O_3 with SO_2 and $(NH_4)_2SO_4$ (Aranyi et al., 1983) produced enhanced effects that can not be attributed to O_3 only.

Early studies in animals exposed to complex mixtures of UV-irradiated auto exhaust containing oxidant concentrations of 0.2 to 1.0 ppm demonstrated a greater number of effects compared to those reported for nonirradiated exhaust (Chapter 9, Section 5.3). No significant differences were found in the magnitude of the response either with or without the presence of sulfur oxides in the mixture. Although the effects described in these studies would be difficult to associate with any particular oxidant species, they are qualitatively similar to the general effects described for exposure to O_3 alone.

One of the major limitations of field and epidemiological studies includes the interference of other pollutants or potential interactions between O_3 and other pollutants in the environment, therefore limiting the usefulness of these studies for standard-setting. Concerns raised about the relative contribution to untoward effects by pollutants other than O_3 have been diminished somewhat by direct comparative findings in exercising athletes showing no differences in response between chamber exposures to oxidant-polluted ambient air or to purified air containing an equivalent concentration of generated O_3 (Avol et al., 1984). Nevertheless, there is still concern that combinations of oxidant pollutants, including precursors of oxidants, may contribute to the decreased function and exacerbation of symptoms reported in asthmatics (Whittemore and Korn, 1980; Linn et al., 1980, 1983a; Lebowitz et al., 1982, 1983, 1985; Lebowitz, 1984; Holguin et al., 1985) and in children and young adults (Lippmann et al., 1983; Lebowitz et al., 1982, 1983, 1985; Bock et al., 1985; Lioy et al., 1985). Possible interactions between O_3 and total suspended particulate matter have been reported with decreased expiratory flow in children (Lebowitz et al., 1982, 1983, 1985; Lebowitz, 1984) and adults with symptoms of airway obstructive disease (Lebowitz et al., 1982, 1983).

The effects of interactions between inhaled oxidant gases and other environmental pollutants on the lung have not been systematically studied. In fact, one of the major problems with the available literature on interaction concerns the exposure design. Most of the controlled studies have not used concentrations of combined pollutants that are found in the ambient environment. In addition, no studies have been reported that used exposure regimens for combined pollutants that are more representative of ambient ratios of peak concentrations, frequency, duration, and time intervals between events, or that examined sequential exposures to individual pollutants.

12.7 IDENTIFICATION OF POTENTIALLY AT-RISK GROUPS

12.7.1 Introduction

The identification of the population or group to be protected by a national ambient air quality standard depends upon a number of factors, including (1) the identification of one or more specific biological endpoints (effects) that individuals within the population should be protected from; and (2) the identification of those individuals in whom those specific pollutant-induced endpoints are (a) observed (b) observed at lower concentrations than in other individuals, (c) observed with greater frequency than in other individuals, (d) have greater consequences than in other individuals, or (e) observed with various combinations of "effects levels," frequency, or consequences. In addition to identification of effects and of groups susceptible to those effects, other factors such as activity patterns and personal habits, as well as actual and potential exposures to the pollutant in question, must be taken into account when identifying one or more groups potentially at risk from exposure to that pollutant.

In the following sections, biological and other factors that have been found to predispose one or more groups to particular risk from exposure to photochemical oxidants are discussed. It should be noted that these factors are discussed in relation to ozone exposure only. There are too few controlled studies with the other oxidants to permit a sound scientific evaluation of their contribution to the toxic action of photochemical oxidant mixtures. Furthermore, all of the controlled studies to date, both in humans and in experimental animals, have utilized non-ozone oxidants at levels one order of magnitude and more above the concentrations measured in ambient air. The health effects of most concern, therefore, are those resulting from exposure to ozone. The following sections also include estimates of the number of individuals in the United States that fall into certain categories of potentially at-risk groups.

It must be emphasized that the final identification of those effects that are considered "adverse" and the final identification of "at-risk" groups are both the domain of the Administrator of the U.S. Environmental Protection Agency.

12.7.2 Potentially At-Risk Individuals

All studies have shown that there is a wide variation in sensitivity to ozone among healthy subjects. The factors suspected of altering sensitivity to ozone are numerous, but those actually known to alter sensitivity are few, largely because few have been examined adequately to determine definitively their effects on sensitivity. The discussion below presents information on the factors that are thought to have the potential for affecting sensitivity to ozone, along with what is actually known from the data regarding the importance of these factors. The terms "sensitivity" and "susceptibility" have been used interchangeably in the Clean Air Act and are also used interchangeably in this discussion.

Sensitivity to a specified dose of an air pollutant may be greater or less than normal. Changes in sensitivity may arise from some prior exposure or may result from cross-reactivity to chemicals. Individual differences in sensitivity or an unusual response upon exposure cannot be explained at the present time. Statistical analysis is generally relied upon to establish the range of normal responses for a particular biological endpoint, and to distinguish between normal responses and those that are indicative of either increased or decreased sensitivity.

Susceptibility may be conferred by some predisposing host factor, such as immunological or biochemical factors; or by some condition, such as preexisting disease. Susceptibility may also result from some aspect of the growth or decline of lung development (e.g., greater bronchomotor tone in childhood, loss of lung function in the elderly), or some previous infectious or immunological process (e.g., childhood respiratory trouble, prior bronchiolitis or other lower respiratory tract infections, and prior asthma). In most human studies, the complex diagnostic procedures needed to classify study subjects properly are not performed, nor is the mechanism of response usually determined or even examined (i.e., underlying immunological, biochemical, or structural character). In epidemiological studies, often not even baseline pulmonary function pulmonary is determined. Furthermore, even diagnostic labels, such as COLD, asthma, allergy, and atopy, are not usually based on sufficient clinical evaluation nor standardized inclusion/exclusion criteria, so that differences in such classifications within and between studies are bound to occur. For example, there are few studies in which bronchoconstrictor challenges, skin or blood antibody testing, or similar procedures were performed, let alone radiographic studies, to characterize disease status.

Airway reactivity is affected by a variety of pharmacologic and non-pharmacologic stimuli. The degree to which different stimuli act in a given individual is determined by a complex set of mechanisms that may vary from subject to subject and from time to time. Unfortunately, little information on these aspects of the study population is available so that reliance must be placed on limited work-ups, non-standardized clinical evaluations and definitions, and theoretical considerations. Thus, estimates of susceptible groups are difficult to assess with any precision with presently available data.

Anthropomorphic and demographic characteristics that have been used to attempt to characterize susceptible individuals in the general population include gender, age, race, ethnic group, nutritional status, baseline lung function, and immunological status. Many of these factors have implications for the acquisition or progress of infectious and chronic diseases. For example, the very young and very old members of the population, individuals with inadequate nutrition, or individuals with depressed baseline lung function may all be predisposed to susceptibility or sensitivity to ozone. None of these factors, however, has been sufficiently studied in relation to O_3 exposure to give definitive answers.

The most prominent modifier of response to O_3 in the general population is minute ventilation, which increases proportionately with increases in exercise workload. Higher levels of exercise enhance the likelihood of increased frequency of irritative symptoms and decrements in forced expiratory volume and flow. However, even in well-controlled experiments on apparently homogeneous groups of healthy subjects, physiological responses to the same exercise levels and the same O_3 concentrations have been found to vary widely among individuals.

Exposure history may determine susceptibility or sensitivity. Smokers, for example, are more susceptible to impaired defense against infection, have some chronic inflammation in the airways, have cellular damage, and may have altered biochemical/cellular responses (e.g., reduced trypsin inhibitory capacity, neutrophilia, impaired macrophage activity). Likewise, those with "significant" occupational exposures to irritants, sensitizers or allergens may have similar predispositions. Furthermore, both groups show differential immunological status, atopy, and, in some cases, bronchomotor tone. Despite these inferences, there is some evidence to suggest that smokers may be less sensitive to O_3, although the available data are not conclusive.

Social, cultural, and economic factors, especially as they affect nutritional status (e.g., vitamin E intake, anemia), may be important. While animal studies with vitamin E indicate that differential responses may be related to nutrition, no evidence exists to indicate that man would benefit from increased vitamin E intake in relation to ambient ozone exposures.

Another determinant of sensitivity is preexisting disease. Asthmatics, who have variable airflow obstruction or reversible airway reactivity, or both, and who may have altered immunological states (e.g., atopy, increased immunoglobulin-E, possibly altered prostaglandin function and/or T-cell function) or cellular function (e.g., eosinophilia), may be expected to be potentially more sensitive to O_3. Asthma, however, is not a specific homogeneous disease and efforts to define asthma precisely have been unsuccessful. Likewise, allergic individuals, with a predisposing atopy, have altered immunological responses, similar to those in asthmatics, and may have labile bronchomotor tone, such that they may also be expected to be potentially more sensitive to O_3. Patients with COLD may be expected to have a variable sensitivity to O_3, since they exhibit a wide diversity of clinical and functional states (see Section 12.4.1). Although currently available evidence indicates that individuals with preexisting disease respond to O_3 exposure to a similar degree as normal subjects, appropriate inclusion and exclusion criteria for selection of these subjects, especially better clinical diagnoses validated by pulmonary function, must be considered before their sensitivity to O_3 can be adequately determined. Furthermore, it should be noted that ethical constraints have precluded the testing in controlled studies of individuals with severe preexisting disease. It is also prudent to consider carefully whether small functional changes in individuals with COLD, asthma, or allergy represent equivalent or more severe physiological significance compared to the normal subject.

12.7.3 Potentially At-Risk Groups

As the preceding discussion and discussions in Sections 12.3 and 12.4 indicate, only small samples of the population, either of healthy individuals or those with preexisting disease, have been tested. Definitive data on the relative susceptibilities to ozone of various kinds of individual subjects are therefore lacking, both in epidemiological and controlled-exposure studies. Notwithstanding the uncertainties that exist in the data, it is possible to identify the groups that might be at potential risk from ozone-induced effects if exposed under certain conditions. The following discussion deals with potential risk only, not actual risk. Actual risk must be estimated (1) in conjunction with actual exposure to ozone, as opposed to potential exposure; (2) in conjunction with any factors known to modify the effects of ozone, such as exercise; and (3) in conjunction with the existing uncertainties in the data on the effects of ozone from controlled, field, or epidemiologic studies.

In the legislative history of Section 109 of the Clean Air Act (U.S. Senate, 1970), the definition of a "sensitive population" excludes "individuals who are otherwise dependent on a controlled internal environment" but includes "particularly sensitive citizens . . . who in the normal course of daily activity are exposed to the ambient environment." Early research demonstrated that the respiratory system is affected by exposure to certain air pollutants, including ozone, nitrogen dioxide, and other oxidants. As a consequence, Congress took note of pollutant effects on the respiratory system and gave bronchial asthmatics and emphysematics as examples of "particularly sensitive" individuals. With regard to research on health effects, Congress has noted that attention should go beyond "normal segments of the population to effects on the very young, the aged, the infirm, and other susceptible individuals." Concern should be given to the "contribution of age, ethnic, social, occupational, smoking, and other factors to susceptibility to air pollution agents."

Consonant with the provisions of the Clean Air Act and with its legislative history, the first group that appears to be at potential risk from exposure to ozone is that group of the general population characterized as having preexisting respiratory disease. In the case of asthmatics, in particular, emerging data from controlled studies indicate no greater responsiveness to ozone in mild asthmatics than in the normal, healthy population. Data from epidemiological studies continue to introduce an element of uncertainty regarding the potential risk from exposure to ambient air in asthmatics. The epidemiological studies, however, lack definitive information on the effects of ozone alone, since there is confounding by the presence of other pollutants (e.g., inhalable particles) and environmental conditions (e.g., temperature) in ambient air (see Section 12.4.2). Furthermore, it must be emphasized that neither controlled nor epidemiological or field studies give any indication that asthmatics are less responsive to ozone exposure than healthy individuals. In the case of individuals with COLD, clinical and functional states vary widely, and responsiveness to ozone exposure may also vary accordingly (see Section 12.4.1).

Nevertheless, several important considerations place individuals with preexisting respiratory disease among groups at potential risk from exposure to ozone. First, it must be noted that concern with triggering untoward reactions has necessitated the use of low concentrations and low exercise levels in most studies on subjects with preexisting disease as well as the involvement only of subjects clinically diagnosed as having mild-to-moderate, but not severe, disease. As a result, few or no data on responses at higher concentrations, at higher exercise levels, or in subjects with more severe disease states are available for comparison with responses in normal subjects. Second, subjects in controlled studies may not have been adequately characterized in all instances regarding disease state. Thus, definitive data on the modification by preexisting disease of responses to ozone are not available. Third, the effects that ozone may have on groups with preexisting disease may not be measured by traditional tests of lung function and the identification of such effects may require the use of different tests or may have to await new technological developments. Finally, it must be emphasized that in individuals with already compromised pulmonary function, the decrements in function produced by exposure to ozone, while similar to or even the same as those experienced by normal subjects, represent a further decline in volumes and flows that are already diminished. It is possible that such declines may impair further the ability to perform normal activities involving exercise. Although many individuals with preexisting disease would not be expected to exercise at the levels at which healthy individuals exercise, any increase in activity level would bring about a commensurate increase in minute ventilation, which is a potentiator of ozone-induced effects. In individuals with preexisting diseases such as asthma or allergies, increases in symptoms upon exposure to ozone, above and beyond symptoms seen in the general population, may also impair or further curtail the ability to function normally.

The second group at potential risk from exposure to ozone consists of the general population of normal, healthy individuals (i.e., not diagnosed as having preexisting respiratory disease). Data presented in Chapter 10 and discussed in preceding sections of this chapter indicate that two factors place members of the general population at potential risk from exposure to ozone: (1) unusual responsiveness to ozone in some members of the general population; and (2) potentiation by exercise of the effects induced by ozone at any given concentration.

Unusual responsiveness to ozone has been observed in some individuals ("responders"), not yet characterized medically except by their response to ozone, who experience greater decrements in lung function from exposure to ozone than the average response of the groups studied. It is not known if "responders" are a specific population subgroup or simply represent the upper 5 to 20 percent of the ozone response distribution. As yet no means of determining in advance those members of the general population who are "responders" has been devised. It is important to note here what has been discussed previously in this chapter and in Chapter 10; that is, the group means presented in Chapter 10 (and the references therein) and in Figures 12-2 through 12-5 (and Table 12-3) include values for the "responders" in the respective study cohorts of otherwise healthy, normal subjects; and reflect the sometimes dramatic decrements seen in those individuals.

Data presented in Chapter 10 and in this chapter underscore the importance of exercise in the potentiation of effects from exposure to ozone. Thus, the general population potentially at risk from exposure to ozone includes those individuals whose activities out of doors, whether vocational or avocational, result in increases in minute ventilation. As stated in section 12.7.2, "the most prominent modifier of response to O_3 in the general population is minute ventilation, which increases proportionately with increases in exercise workload."

As pointed out in this chapter, other biological and nonbiological factors are suspected of influencing responses to ozone. Data remain inconclusive at the present, however, regarding the importance of age, gender, and other factors in influencing response to ozone. Thus, at the present time, no groups are thought to be at potential risk from exposure to ozone in ambient air through biological predisposition or activity patterns other than those identified in this section.

12.7.4 Demographic Distribution of the General Population

The U.S. Bureau of the Census periodically provides an updated statistical summary of the U.S. population by conducting a decennial survey, supplemented by monthly surveys of representative population samples. The complete census represents a total count of the population since an attempt is made to account for the social, economic, and housing characteristics of every residence. In determining residence, the census counts the place where eating and sleeping usually take place rather than counting a person's legal or voting residence. Each residence is, in turn, grouped according to the official standard metropolitan statistical areas (SMSA's) and standard consolidated statistical areas (SCSA's) as defined by the Office of Management and Budget. Briefly, SMSA's represent a large population nucleus together with adjacent communities which have a high degree of social and economic integration; SCSA's are large metropolitan complexes consisting of groups of closely related adjacent SMSA's. Table 12-6 gives the geographical distribution of the resident population of the United States for 1980 (U.S. Bureau of the Census, 1982). The entire territory of the United States is classified as metropolitan (inside SMSA's) or nonmetropolitan (outside SMSA's). According to the 1980 census, the urban population comprises all persons living in cities, villages, boroughs, and towns of 2500 or more inhabitants. Additional data on age, sex, and race obtained from the 1980 census are shown in Table 12-7. Evaluation of previous census data indicated a total net underenumeration rate of about 2.2 percent in 1970 and 2.7 percent in 1960. Although estimates for 1980 have not been published, preliminary results indicated that overall coverage improved in the 1980 census. Census data presented in Tables 12-6 and 12-7 have not been adjusted for underenumeration.

12.7.5 Demographic Distribution of Individuals with Chronic Respiratory Conditions

Certain subpopulations have been identified as potentially-at-risk to ozone or photochemical oxidant exposure by virtue of preexisting respiratory conditions like chronic obstructive lung disease (COLD) and asthma. Each year the National Health Interview Survey (HIS) conducted by the National Center for Health Statistics (NCHS) reports the prevalence of chronic respiratory conditions in the United States. These conditions are classified by type, according to the Ninth Revision of the International Classification of Diseases adopted for use in the United States (World Health Organization, 1977). According to NCHS, a condition was considered to be chronic if it had been documented by a physician more than three months before the interview was conducted. In the HIS for 1979 (U.S. Department of Health and Human Services, 1981) COLD was not listed as a specific medical condition since it is a clinical term and not generally recognized by the general public. However, this term has been used with increasing frequency by physicians rather than the more common terms chronic bronchitis and emphysema in classifying chronic airways obstruction. As a result, there may be an underestimation by the HIS of the true prevalence of this disorder.

TABLE 12-6. GEOGRAPHICAL DISTRIBUTION OF THE RESIDENT POPULATION OF THE UNITED STATES, 1980[a]

Residence	Population, millions	Population, percent
Total	226.5	100.0
Northeast	49.1	21.7
North Central	58.9	26.0
South	75.4	33.3
West	43.2	19.0
Metropolitan areas[b]	169.4	74.8
Central cities	68.0	30.0
Outside central cities	101.5	44.8
Nonmetropolitan areas	57.1	25.2
Urban[c]	167.1	73.7
Rural	59.5	26.3

[a] U.S. Bureau of the Census (1982).

[b] Represented by 318 standard metropolitan statistical areas (SMSA's).

[c] Comprises all persons living in cities, villages, boroughs, and towns of 2500 or more inhabitants but excluding those persons living in the rural portions of extended cities.

The estimated prevalence of chronic bronchitis, emphysema, and asthma in the United States is shown in Table 12-8 for the year 1979 (U.S. Department of Health and Human Services, 1981). All three respiratory conditions combined accounted for over 16 million individuals in 1979, representing 7.5 percent of the population. Approximately one-third of the individuals with chronic bronchitis and asthma were under 17 years of age. An additional 15 to 16 million persons reported having hay fever and other upper respiratory allergies. Accounting for an underestimation by the HIS, the total number of individuals with documented and undocumented respiratory conditions in the United States may be as high as 47 million, which is approximately 0 percent of the population.

TABLE 12-7. TOTAL POPULATION OF THE UNITED STATES BY AGE, SEX, AND RACE, 1980[a]

Age, sex, race	Population, millions	Population, percent
Total	226.5	100.0
Under 5 years	16.3	7.2
5-17 years	47.1	20.8
18-44 years	93.3	41.2
45-64 years	44.4	19.6
65 years and over	25.5	11.3
Male	110.0	48.6
Female	116.5	51.4
White[b]	194.8	86.0
Black[b]	26.6	11.7
Other[b]	5.1	2.3

[a] U.S. Bureau of the Census (1982).

[b] Data represent self-classification according to 15 groups listed on the 1980 census questionnaire: White, Black, American, Indian, Eskimo, Aleut, Chinese, Filipino, Japanese, Asian Indian, Korean, Vietnamese, Hawaiian, Samoan, Guamanian, and Other.

12.8 SUMMARY AND CONCLUSIONS

12.8.1 Health Effects in the General Human Population

Controlled human studies of at-rest exposures to O_3 lasting 2 to 4 hr have demonstrated decrements in forced expiratory volume and flow occurring at and above 0.5 ppm of O_3 (Chapter 10). Airway resistance was not significantly changed at these O_3 concentrations. Breathing O_3 at rest at concentrations $<$ 0.5 ppm did not significantly impair pulmonary function although the occurrence of some O_3-related pulmonary symptoms has been suggested in a number of studies.

One of the principal modifiers of the magnitude of response to O_3 is minute ventilation ($\dot{V}_E$), which increases proportionately with increases in exercise work load. Adjustment by the respiratory system to an increased work load is characterized by increased frequency and depth of breathing. Consequent increases in $\dot{V}_E$ not only increase the overall volume of inhaled pollutant, but the increased tidal volume may lead to a higher concentration of ozone in the

TABLE 12-8. PREVALENCE OF CHRONIC RESPIRATORY CONDITIONS BY SEX AND AGE FOR 1979[a]

Condition[b]	Number of persons, in thousands							
	Total[c]	Male	Female	<17 years old	17-44 years old	45-64 years old	>65 years old	% of U.S. population
Chronic bronchitis	7474	3289	4175	2458	2412	1547	1060	3.5
Emphysema	2137	1364	770	12[d]	127[d]	1008	990	1.0
Asthma[e]	6402	3113	3293	2225	2203	1482	488	3.0
Hay fever and other upper respiratory allergies[f]	15,620	7027	8584	3151	8278	3012	1181	7.2

[a] U.S. Department of Health and Human Services, 1981.

[b] Classified by type, according to the Ninth Revision of the International Classific of Diseases (World Health Organization, 1977).

[c] Reported as actual number in thousands; remaining subsets have been calculated from percentages and are rounded off.

[d] Does not meet standards of reliability or precision set by the National Center for Health Statistics (more than 30% relative standard error).

[e] With or without hay fever.

[f] Without asthma.

lung regions most sensitive to ozone. These processes are further enhanced at high work loads ($\dot{V}_E > 35$ L/min), since the mode of breathing changes at that $\dot{V}_E$ from nasal to oronasal.

Statistically significant decrements in forced expiratory volume and flow are generally observed in healthy adult subjects (18 to 45 yr old) after 1 to 3 hr of exposure as a function of the level of exercise performed and the ozone concentration inhaled during the exposure. Group mean data pooled from numerous controlled human exposure (Chapter 10) and field (Chapter 11) studies indicate that, on average, pulmonary function decrements occur:

1. At $\geq$0.37 ppm O_3 with light exercise ($\dot{V}_E \leq 23$ L/min);
2. At $\geq$0.30 ppm O_3 with moderate exercise ($\dot{V}_E = 24$-43 L/min);
3. At $\geq$0.24 ppm O_3 with heavy exercise ($\dot{V}_E = 44$-63 L/min); and
4. At $\geq$0.18 ppm O_3 with very heavy exercise ($\dot{V}_E \geq 64$ L/min).

Note, however, that data from specific individual studies indicate that pulmonary function decrements occur with very heavy exercise in healthy adults at 0.15 to 0.16 ppm O_3 (Avol et al., 1984) and suggest that such effects may occur in healthy adults at levels as low as 0.12 ppm O_3 (McDonnell et al., 1983). Also, pulmonary function decrements have been observed in children and adolescents at concentrations of 0.12 and 0.14 ppm O_3 with heavy exercise (McDonnell et al., 1985b; Avol et al., 1985a). At the lower O_3 concentrations (0.12 to 0.15 ppm), the average changes in lung function are generally small ($\leq$5 percent) and are a matter of controversy in regard to their medical significance.

In the majority of the studies reported, 15-min intermittent exercise alternated with 15-min rest was employed for the duration of the exposure. Figure 12-6 uses the pulmonary function measurement FEV_1 to illustrate the effects of intermittent exercise and O_3 concentration during 2-hr exposures. As noted above, larger decrements in lung function occur at higher exercise levels and at higher O_3 concentrations. The maximum response to O_3 exposure can be observed within 5 to 10 min following the end of each exercise period. Other measures of spirometric pulmonary function (e.g., FVC and $FEF_{25-75\%}$) are consistent with FEV_1 and, therefore, are not depicted here. It is important to note, however, that any predictions of average pulmonary function responses to O_3 only apply under the specific set of exposure conditions at which these data were derived.

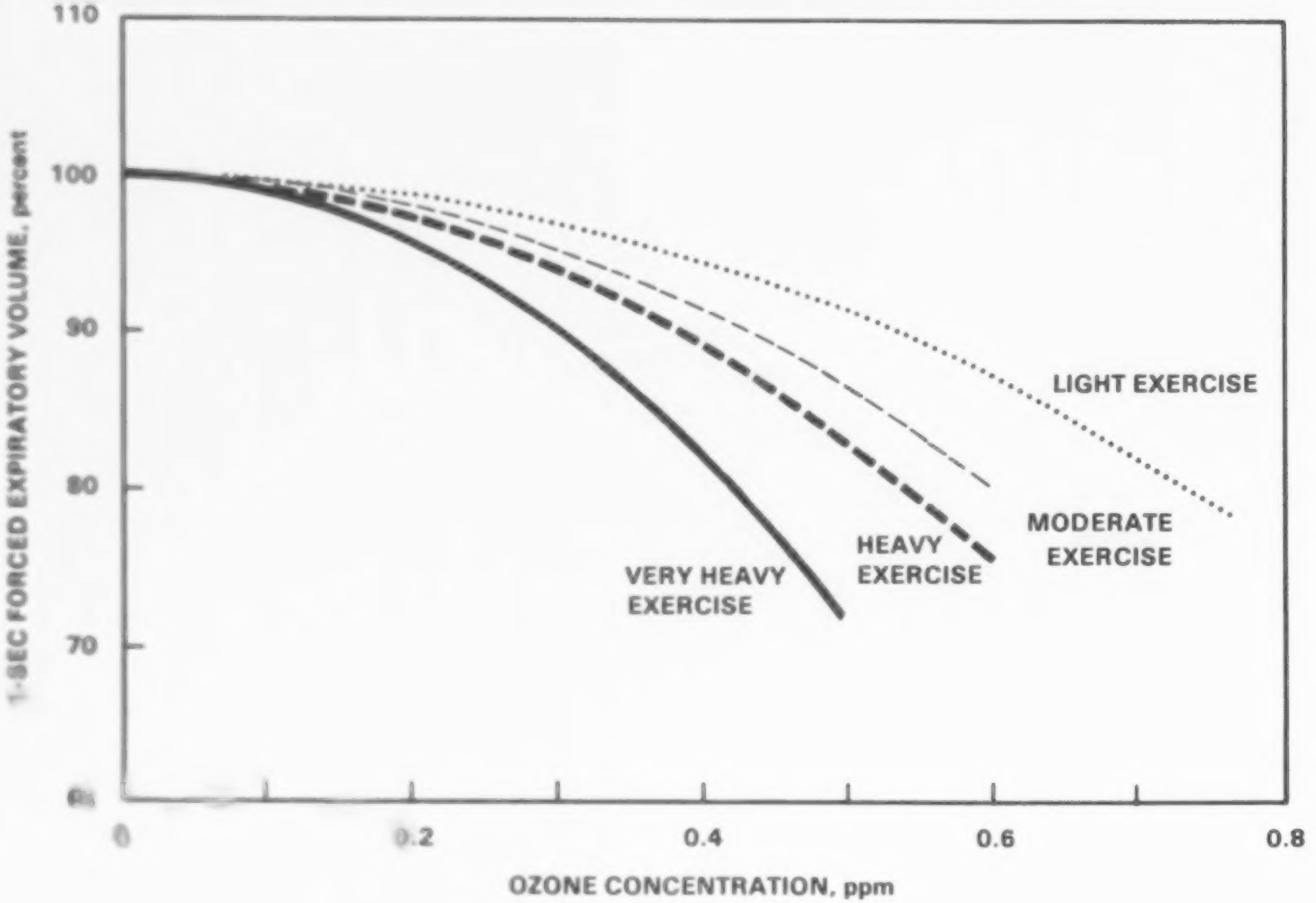

Figure 12-6. Group mean decrements in 1-sec forced expiratory volume during 2-hr ozone exposures with different levels of intermittent exercise: light ($\dot{V}_E \leqslant 23$ L/min); moderate ($\dot{V}_E$ = 24-43 L/min); heavy ($\dot{V}_E$ = 44-63 L/min); and very heavy ($\dot{V}_E \geqslant 64$ L/min). Concentration-response curves are taken from Figures 12-2 through 12-5.

Continuous exercise equivalent in duration to the sum of intermittent exercise periods at comparable ozone concentrations (0.2 to 0.4 ppm) and minute ventilation (60 to 80 L/min) seems to elicit greater changes in pulmonary function (Folinsbee et al., 1984; Avol et al., 1984, 1985c) but the differences between intermittent and continuous exercise are not clearly established. More experimental data are needed to make any quantitative evaluation of the differences in effects induced by these two modes of exercise.

Functional recovery, at least from a single exposure with exercise, appears to progress in two phases: during the initial rapid phase, lasting between 1 and 3 hr, pulmonary function improves more than 50 percent; this is followed by a much slower recovery that is usually completed in most subjects within 24 hr. In some individuals, an enhanced responsiveness to a second O_3 challenge may persist for up to 48 hr (Bedi et al., 1985; Folinsbee and Horvath, 1986). In addition, despite apparent functional recovery, other regulatory systems may still exhibit abnormal responses when stimulated; e.g., airway hyperreactivity may persist for days.

Group mean changes may be useful for making statistical inferences about homogeneous populations, but they are not adequate for describing differences in responsiveness to O_3 among individuals. Even in well-controlled experiments on an apparently homogeneous group of healthy subjects, physiological responses to the same work and pollutant loads will vary widely among individuals (Horvath et al., 1981; Gliner et al., 1983; McDonnell et al., 1983; Kulle et al., 1985). Despite large intersubject variability, individual responsiveness to a given O_3 concentration is quite reproducible (Gliner et al., 1983; McDonnell et al., 1985a). Some individuals, therefore, are consistently more responsive to O_3 than are others. The term "responders" has been used to describe the 5 to 20 percent of the studied population that is most responsive to O_3 exposure. There are no clearly established criteria to define this group of subjects. Likewise, there are no known specific factors responsible for increased or decreased responsiveness to O_3. Characterization of individual responses to O_3, however, is pertinent since it permits the assessment of a segment of the general population that is potentially at-risk to O_3 exposure (see Section 12.7.3) although statistical treatment of these data is still rudimentary and their validity is open to question.

A close association has been observed between the occurrence of respiratory symptoms and changes in pulmonary function in adults acutely exposed in environmental chambers to O_3 (Chapter 10) or to ambient air containing O_3 as the predominant pollutant (Chapter 11). This association holds for both the time-course and magnitude of effects. Studies on children and adolescents exposed to O_3 or ambient air containing O_3 under similar conditions have found no significant increases in symptoms despite significant changes in pulmonary function (Avol et al., 1985a,b; McDonnell et al., 1985b,c). Epidemiological studies of exposure to ambient photochemical pollution are of limited use for quantifying exposure-response relationships for O_3 because they have not adequately controlled for other pollutants, meteorological variables, and non-environmental factors in the data analysis. Eye irritation, for example, one of the most common complaints associated with photochemical pollution, is not characteristic of clinical exposures to O_3, even at concentrations several times higher than any likely to be encountered in ambient air. There is limited qualitative evidence to suggest that at low concentrations of O_3, other respiratory and nonrespiratory symptoms, as well, are more likely to occur in populations exposed to ambient air pollution than in subjects exposed in chamber studies (Chapter 11).

Discomfort caused by irritative symptoms may be responsible for the impairment of athletic performance reported in high school students during cross-country track meets in Los Angeles (Chapter 11). Only a few controlled-exposure studies, however, have been designed to examine the effects of O_3 on exercise performance (Chapter 10). In one study, light intermittent exercise ($\dot{V}_E$ = 20-25 L/min) at a high O_3 concentration (0.75 ppm) reduced postexposure maximal exercise capacity by limiting maximal oxygen consumption; submaximal oxygen consumption changes were not significant. The extent of ventilatory and respiratory metabolic changes observed during or following the exposure appears to have been related to the magnitude of pulmonary function impairment. Whether such changes are consequent to respiratory discomfort (i.e., symptomatic effects) or are the result of changes in lung mechanics or both is still unclear and needs to be elucidated.

Environmental conditions such as heat and relative humidity may alter subjective symptoms and physiological impairment associated with O_3 exposure. Modification of the effects of O_3 by these factors may be attributed to increased ventilation associated with elevated body temperature but there may also be an independent effect of elevated body temperature on pulmonary function (VC).

Numerous additional factors have the potential for altering responsiveness to ozone. For example, children and older individuals may be more responsive than young adults. Other factors such as gender differences (at any age), personal habits such as smoking, nutritional deficiencies, or differences in immunologic status may predispose individuals to susceptibility to ozone. In addition, social, cultural, or economic factors may be involved. Those actually known to alter sensitivity, however, are few, largely because they have not been examined adequately to determine definitively their effects on sensitivity to O_3. The following briefly summarizes what is actually known from the data regarding the importance of these factors (see Section 12.3.3 for details):

1. Age. Although changes in growth and development of the lung with age have been postulated as one of many factors capable of modifying responsiveness to O_3, sufficient numbers of studies have not been performed to provide any sound conclusions for effects of different age groups on responsiveness to O_3.

2. Sex. Sex differences in responsiveness to ozone have not been adequately studied. Lung function of women, as assessed by changes in $FEV_{1.0}$, might be affected more than that of men under similar exercise and exposure conditions, but the possible differences have not been tested systematically.

3. Smoking Status. Differences between smokers and nonsmokers have been studied often, but the smoking histories of subjects are not documented well. There is some evidence, however, to suggest that smokers may be less responsive to O_3 than nonsmokers.

4. Nutritional Status. Antioxidant properties of vitamin E in preventing ozone-initiated peroxidation *in vitro* are well demonstrated and their protective effects *in vivo* are clearly demonstrated in rats and mice. No evidence indicates, however, that man would benefit from increased vitamin E intake relative to ambient ozone exposures.

5. Red Blood Cell Enzyme Deficiencies. There have been too few studies performed to document reliably that individuals with a hereditary deficiency of glucose-6-phosphate dehydrogenase may be at-risk to significant hematological effects from O_3 exposure. Even if O_3 or a reactive product of O_3-tissue

interaction were to penetrate the red blood cell after *in vivo* exposure, it is unlikely that any depletion of glutathione or other reducing compounds would be of functional significance for the affected individual.

Successive daily brief exposures of healthy human subjects to O_3 (<0.7 ppm for approximately 2 hr) induce a typical temporal pattern of response (Chapter 10, Section 10.3). Maximum functional changes that occur after the first or second exposure day become progressively attenuated on each of the subsequent days. By the fourth day of exposure, the average effects are not different from those observed following control (air) exposure. Individuals need between 3 and 7 days of exposure to develop full attenuation, with more sensitive subjects requiring more time. The magnitude of a peak response to O_3 appears to be directly related to O_3 concentration. It is not known how variations in the length or frequency of exposure will modify the time course of this altered responsiveness. In addition, concentrations of O_3 that have no detectable effect appear not to invoke changes in response to subsequent exposures at higher O_3 concentrations. Full attenuation, even in ozone-sensitive subjects, does not persist for more than 3 to 7 days after exposure in most individuals, while partial attenuation might persist for up to 2 weeks. Although the severity of symptoms is generally related to the magnitude of the functional response, partial attenuation of symptoms appears to persist longer, for up to 4 weeks after exposure.

Whether populations exposed to photochemical air pollution develop at least partial attenuation is unknown. No epidemiological studies have been designed to test this hypothesis and additional information is required from controlled laboratory studies before any sound conclusions can be made.

Ozone toxicity, in both humans and laboratory animals, may be mitigated through altered responses at the cellular and/or subcellular level. At present, the mechanisms underlying altered responses are unclear and the effectiveness of such mitigating factors in protecting the long-term health of the individual against ozone is still uncertain. A growing body of experimental evidence suggests the involvement of vagal sensory receptors in modulating the acute responsiveness to ozone. It is highly probable that most of the decrements in lung volume reported to result from exposures of greatest relevance to standard-setting ($\leq$0.3 ppm O_3) are caused by the inhibition of maximal inspiration rather than by changes in airway diameter. None of the experimental evidence, however, is definitive and additional research is needed to elucidate the precise mechanism(s) associated with ozone exposure.

12.8.2 Health Effects in Individuals with Preexisting Disease

Currently available evidence indicates that individuals with preexisting disease respond to O_3 exposure to a similar degree as normal, healthy subjects. Patients with chronic obstructive lung disease and/or asthma have not shown increased responsiveness to O_3 in controlled human exposure studies, but there is some indication from epidemiological studies that asthmatics may be symptomatically and possibly functionally more responsive than healthy individuals to ambient air exposures. Appropriate inclusion and exclusion criteria for selection of these subjects, however, especially better clinical diagnoses validated by pulmonary function, must be considered before their responsiveness to O_3 can be adequately determined. None of these factors has been sufficiently studied in relation to O_3 exposures to give definitive answers.

12.8.3 Extrapolation of Effects Observed in Animals to Human Populations

Animal experiments on a variety of species have demonstrated increased susceptibility to bacterial respiratory infections following O_3 exposure. Thus, it could be hypothesized that humans exposed to O_3 could experience decrements in their host defenses against infection. At the present time, however, these effects have not been studied in humans exposed to O_3.

Animal studies have also reported a number of extrapulmonary responses to O_3, including cardiovascular, reproductive, and teratological effects, along with changes in endocrine and metabolic function. The implications of these findings for human health are difficult to judge at the present time. In addition, central nervous system effects, alterations in red blood cell morphology and enzymatic activity, as well as cytogenetic effects on circulating lymphocytes, have been observed in laboratory animals following exposure to O_3. While similar effects have been described in circulating cells from human subjects exposed to high concentrations of O_3, the results were either inconsistent or of questionable physiological significance (Section 12.3.8). It is not known, therefore, if extrapulmonary responses would be likely to occur in humans when exposure schedules are used that are representative of exposures that the population at large might actually experience.

Despite wide variations in study techniques and experimental designs, acute and subchronic exposures of animals to levels of ozone < 0.5 ppm produce remarkably similar types of responses in all species examined. A characteristic ozone lesion occurs at the junction of the conducting airways and the gas-exchange regions of the lung after acute O_3 exposure. Dosimetry model simulations predict that the maximal tissue dose of O_3 occurs in this region of the lung. Continuation of the inflammatory process during longer O_3 exposures is especially important since it appears to be correlated with increased airway resistance, increased lung collagen content, and remodeling of the centriacinar airways, suggesting the development of distal airway narrowing. No convincing evidence of emphysema in animals chronically exposed to O_3 has yet been published, but centriacinar inflammation has been shown to occur.

Since substantial animal data exist for O_3-induced changes in lung structure and function, biochemistry, and host defenses, it is conceivable that man may experience more types of effects from exposure to ozone than have been established in human clinical studies. It is important to note, however, that the risks to man from breathing ambient levels of ozone cannot fully be determined until quantitative extrapolations of animal results can be made.

12.8.4 Health Effects of Other Photochemical Oxidants and Pollutant Mixtures

Controlled human studies have not consistently demonstrated any modification of respiratory effects for combined exposures of O_3 with SO_2, NO_2, CO, or H_2SO_4 and other particulate aerosols. Ozone alone is considered to be responsible for the observed effects of those combinations or of multiple mixtures of these pollutants. Combined exposure studies in laboratory animals have produced varied results, depending upon the pollutant combination evaluated, the exposure design, and the measured variables (Section 12.6.3). Thus, no definitive conclusions can be drawn from animal studies of pollutant interactions. There have been far too few controlled toxicological studies with other oxidants, such as peroxyacetyl nitrate or hydrogen peroxide, to permit a sound scientific evaluation of their contribution to the toxic action of photochemical oxidant mixtures. There is still some concern, however, that combinations of oxidant pollutants with other pollutants may contribute to the symptom aggravation and decreased lung function described in epidemiological studies on individuals with asthma and in children and young adults. For this reason, the effects of interaction between inhaled oxidant gases and other environmental pollutants on the lung need to be systematically studied using exposure regimens that are more closely representative of ambient air ratios of peak concentrations, frequency, duration, and time intervals between events.

12.8.5 Identification of Potentially At-Risk Groups

Despite uncertainties that may exist in the data, it is possible to identify the groups that may be at potential risk from exposure to ozone, based on known health effects, activity patterns, personal habits, and actual or potential exposures to ozone.

The first group that appears to be at potential risk from exposure to ozone is that group of the general population characterized as having preexisting respiratory disease. Available data on actual differences in responsiveness between these and healthy members of the general population indicate that, under the exposure conditions studied to date, individuals with preexisting disease are as responsive to ozone as healthy individuals. Nevertheless, two primary considerations place individuals with preexisting respiratory disease among groups at potential risk from exposure to ozone. First, it must be noted that concern with triggering untoward reactions has necessitated the use of low concentrations and low exercise levels in most studies on subjects with mild, but not severe, preexisting disease. Therefore, few or no data on responses at higher concentrations, at higher exercise levels, and in subjects with more severe disease states are available for comparison with responses in healthy subjects. Thus, definitive data on the modification by preexisting disease of responses to ozone are not available. Second, however, it must be emphasized that in individuals with already compromised pulmonary function, the decrements in function produced by exposure to ozone, while similar to or even the same as those experienced by normal subjects, represent a further decline in volumes and flows that are already diminished. It is possible that such declines may impair further the ability to perform normal activities. In individuals with preexisting diseases such as asthma or allergies, increases in symptoms upon exposure to ozone, above and beyond symptoms seen in the general population, may also impair or further curtail the ability to function normally.

The second group at potential risk from exposure to ozone consists of the general population of normal, healthy individuals. Two specific factors place members of the general population at potential risk from exposure to ozone. First, unusual responsiveness to ozone has been observed in some individuals ("responders"), not yet characterized medically except by their response to ozone, who experience greater decrements in lung function from exposure to ozone than the average response of the groups studied. It is not known if "responders" are a specific population subgroup or simply represent the upper 5 to 20 percent of the ozone response distribution. As yet no means of determining in advance those members of the general population who are "responders" has been devised. Second, data presented in this chapter underscore the importance of exercise in the potentiation of effects from exposure to ozone. Thus, the general population potentially at risk from exposure to ozone includes those individuals whose activities out of doors, whether vocational or avocational, result in increases in minute ventilation, which is the most prominent modifier of response to ozone.

Other biological and nonbiological factors have the potential for influencing responses to ozone. Data remain inconclusive at the present, however, regarding the importance of age, gender, and other factors in influencing response to ozone. Thus, at the present time, no other groups are thought to be biologically predisposed to increased sensitivity to ozone. It must be emphasized, however, that the final identification of those effects that are considered "adverse" and the final identification of "at-risk" groups are both the domain of the Administrator of the U.S. Environmental Protection Agency.

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APPENDIX A: GLOSSARY OF PULMONARY TERMS AND SYMBOLS*

Acetylcholine (ACh): A naturally occurring substance in the body having important parasympathetic effects; often used as a bronchoconstrictor.

Aerosol: Solid particles or liquid droplets that are dispersed or suspended in a gas, ranging in size from 10^{-4} to 10^{2} micrometers (μm).

Air spaces: All alveolar ducts, alveolar sacs, and alveoli. To be contrasted with AIRWAYS.

Airway conductance (Gaw): Reciprocal of airway resistance. Gaw = (1/Raw).

Airway resistance (Raw): The (frictional) resistance to airflow afforded by the airways between the airway opening at the mouth and the alveoli.

Airways: All passageways of the respiratory tract from mouth or nares down to and including respiratory bronchioles. To be contrasted with AIR SPACES.

Allergen: A material that, as a result of coming into contact with appropriate tissues of an animal body, induces a state of allergy or hypersensitivity; generally associated with idiosyncratic hypersensitivities.

Alveolar-arterial oxygen pressure difference [$P(A-a)O_2$]: The difference in partial pressure of O_2 in the alveolar gas spaces and that in the systemic arterial blood, measured in torr.

Alveolar-capillary membrane: A fine membrane (0.2 to 0.4 μm) separating alveolus from capillary; composed of epithelial cells lining the alveolus, a thin layer of connective tissue, and a layer of capillary endothelial cells.

Alveolar carbon dioxide pressure (P_ACO_2): Partial pressure of carbon dioxide in the air contained in the lung alveoli.

Alveolar oxygen partial pressure (P_AO_2): Partial pressure of oxygen in the air contained in the alveoli of the lungs.

Alveolar septum (pl. septa): A thin tissue partition between two adjacent pulmonary alveoli, consisting of a close-meshed capillary network and interstitium covered on both surfaces by alveolar epithelial cells.

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Alveolitis: (interstitial pneumonia): Inflammation of the lung distal to the terminal non-respiratory bronchiole. Unless otherwise indicated, it is assumed that the condition is diffuse. Arbitrarily, the term is not used to refer to exudate in air spaces resulting from bacterial infection of the lung.

Alveolus: Hexagonal or spherical air cells of the lungs. The majority of alveoli arise from the alveolar ducts which are lined with the alveoli. An alveolus is an ultimate respiratory unit where the gas exchange takes place.

Anatomical dead space ($V_{D\ anat}$): Volume of the conducting airways down to the level where, during air breathing, gas exchange with blood can occur, a region probably situated at the entrance of the alveolar ducts.

Arterial oxygen saturation (SaO_2): Percent saturation of dissolved oxygen in arterial blood.

Arterial partial pressure of carbon dioxide ($PaCO_2$): Partial pressure of dissolved carbon dioxide in arterial blood.

Arterial partial pressure of oxygen (PaO_2): Partial pressure of dissolved oxygen in arterial blood.

Asthma: A disease characterized by an increased responsiveness of the airways to various stimuli and manifested by slowing of forced expiration which changes in severity either spontaneously or as a result of therapy. The term asthma may be modified by words or phrases indicating its etiology, factors provoking attacks, or its duration.

Atelectasis: State of collapse of air spaces with elimination of the gas phase.

ATPS condition (ATPS): Ambient temperature and pressure, saturated with water vapor. These are the conditions existing in a water spirometer.

Atropine: A poisonous white crystalline alkaloid, $C_{17}H_{23}NO_3$, from belladonna and related plants, used to relieve spasms of smooth muscles. It is an anticholinergic agent.

Breathing pattern: A general term designating the characteristics of the ventilatory activity, e.g., tidal volume, frequency of breathing, and shape of the volume time curve.

Breuer-Hering reflexes (Hering-Breuer reflexes): Ventilatory reflexes originating in the lungs. The reflex arcs are formed by the pulmonary mechanoreceptors, the vagal afferent fibers, the respiratory centers, the medullo-spinal pathway, the motor neurons, and the respiratory muscles. The afferent link informs the respiratory centers of the volume state or of the rate of change of volume of the lungs. Three types of Breuer-Hering reflexes have been described: 1) an inflation reflex in which lung inflation tends to inhibit inspiration and stimulate expiration; 2) a deflation reflex in which lung deflation tends to inhibit expiration and stimulate inspiration; and 3) a "paradoxical reflex," described but largely disregarded by Breuer and Hering, in which sudden inflation may stimulate inspiratory muscles.

Bronchiole: One of the finer subdivisions of the airways, less than 1 mm in diameter, and having no cartilage in its wall.

Bronchiolitis: Inflammation of the bronchioles which may be acute or chronic. If the etiology is known, it should be stated. If permanent occlusion of the lumens is present, the term bronchiolitis obliterans may be used.

Bronchitis: A non-neoplastic disorder of structure or function of the bronchi resulting from infectious or noninfectious irritation. The term bronchitis should be modified by appropriate words or phrases to indicate its etiology, its chronicity, the presence of associated airways dysfunction, or type of anatomic change. The term chronic bronchitis, when unqualified, refers to a condition associated with prolonged exposure to nonspecific bronchial irritants and accompanied by mucous hypersecretion and certain structural alterations in the bronchi. Anatomic changes may include hypertrophy of the mucous-secreting apparatus and epithelial metaplasia, as well as more classic evidences of inflammation. In epidemiologic studies, the presence of cough or sputum production on most days for at least three months of the year has sometimes been accepted as a criterion for the diagnosis.

Bronchoconstrictor: An agent that causes a reduction in the caliber (diameter) of airways.

Bronchodilator: An agent that causes an increase in the caliber (diameter) of airways.

Bronchus: One of the subdivisions of the trachea serving to convey air to and from the lungs. The trachea divides into right and left main bronchi which in turn form lobar, segmental, and subsegmental bronchi.

BTPS conditions (BTPS): Body temperature, barometric pressure, and saturated with water vapor. These are the conditions existing in the gas phase of the lungs. For man the normal temperature is taken as 37°C, the pressure as the barometric pressure, and the partial pressure of water vapor as 47 torr.

Carbachol: A parasympathetic stimulant (carbamoylcholine chloride, $C_6H_{15}ClN_2O_2$) that produces constriction of the bronchial smooth muscles.

Carbon dioxide production ($\dot{V}CO_2$): Rate of carbon dioxide production by organisms, tissues, or cells. Common units: ml CO_2 (STPD)/kg·min.

Carbon monoxide (CO): An odorless, colorless, toxic gas formed by incomplete combustion, with a strong affinity for hemoglobin and cytochrome; it reduces oxygen absorption capacity, transport, and utilization.

Carboxyhemoglobin (COHb): Hemoglobin in which the iron is associated with carbon monoxide. The affinity of hemoglobin for CO is about 300 times greater than for O_2.

Chronic obstructive lung disease (COLD): This term refers to diseases of uncertain etiology characterized by persistent slowing of airflow during forced expiration. It is recommended that a more specific term, such as chronic obstructive bronchitis or chronic obstructive emphysema, be used whenever possible. Synonymous with chronic obstructive pulmonary disease (COPD).

Closing capacity (CC): Closing volume plus residual volume, often expressed as a ratio of TLC, i.e. (CC/TLC%).

Closing volume (CV): The volume exhaled after the expired gas concentration is inflected from an alveolar plateau during a controlled breathing maneuver. Since the value obtained is dependent on the specific test technique, the method used must be designated in the text, and when necessary, specified by a qualifying symbol. Closing volume is often expressed as a ratio of the VC, i.e. (CV/VC%).

Collateral resistance (R_{coll}): Resistance to flow through indirect pathways. See COLLATERAL VENTILATION and RESISTANCE.

Collateral ventilation: Ventilation of air spaces via indirect pathways, e.g., through pores in alveolar septa, or anastomosing respiratory bronchioles.

Compliance (C_L,C_{st}): A measure of distensibility. Pulmonary compliance is given by the slope of a static volume-pressure curve at a point, or the linear approximation of a nearly straight portion of such a curve, expressed in liters/cm H_2O or ml/cm H_2O. Since the static volume-pressure characteristics of lungs are nonlinear (static compliance decreases as lung volume increases) and vary according to the previous volume history (static compliance at a given volume increases immediately after full inflation and decreases following deflation), careful specification of the conditions of measurement are necessary. Absolute values also depend on organ size. See also DYNAMIC COMPLIANCE.

Conductance (G): The reciprocal of RESISTANCE. See AIRWAY CONDUCTANCE.

Diffusing capacity of the lung (D_L, D_LO_2, D_LCO_2, D_LCO): Amount of gas (O_2, CO, CO_2) commonly expressed as ml gas (STPD) diffusing between alveolar gas and pulmonary capillary blood per torr mean gas pressure difference per min, i.e., ml O_2/(min-torr). Synonymous with transfer factor and diffusion factor.

Dynamic compliance (C_{dyn}): The ratio of the tidal volume to the change in intrapleural pressure between the points of zero flow at the extremes of tidal volume in liters/cm H_2O or ml/cm H_2O. Since at the points of zero airflow at the extremes of tidal volume, volume acceleration is usually other than zero, and since, particularly in abnormal states, flow may still be taking place within lungs between regions which are exchanging volume, dynamic compliance may differ from static compliance, the latter pertaining to condition of zero volume acceleration and zero gas flow throughout the lungs. In normal lungs at ordinary volumes and respiratory frequencies, static and dynamic compliance are the same.

Elastance (E): The reciprocal of COMPLIANCE; expressed in cm H_2O/liter or cm H_2O/ml.

Electrocardiogram (ECG, EKG): The graphic record of the electrical currents that are associated with the heart's contraction and relaxation.

Emphysema: A condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis.

Expiratory reserve volume (ERV): The maximal volume of air exhaled from the end-expiratory level.

FEV_t/FVC: A ratio of timed (t = 0.5, 1, 2, 3 s) forced expiratory volume (FEV_t) to forced vital capacity (FVC). The ratio is often expressed in percent 100 x FEV_t/FVC. It is an index of airway obstruction.

Flow volume curve: Graph of instantaneous forced expiratory flow recorded at the mouth, against corresponding lung volume. When recorded over the full vital capacity, the curve includes maximum expiratory flow rates at all lung volumes in the VC range and is called a maximum expiratory flow-volume curve (MEFV). A partial expiratory flow-volume curve (PEFV) is one which describes maximum expiratory flow rate over a portion of the vital capacity only.

Forced expiratory flow (FEFx): Related to some portion of the FVC curve. Modifiers refer to the amount of the FVC already exhaled when the measurement is made. For example:

$FEF_{75\%}$ = instantaneous forced expiratory flow after 75% of the FVC has been exhaled.

$FEF_{200-1200}$ = mean forced expiratory flow between 200 ml and 1200 ml of the FVC (formerly called the maximum expiratory flow rate (MEFR).

$FEF_{25-75\%}$ = mean forced expiratory flow during the middle half of the FVC [formerly called the maximum mid-expiratory flow rate (MMFR)].

FEF_{max} = the maximal forced expiratory flow achieved during an FVC.

Forced expiratory volume (FEV): Denotes the volume of gas which is exhaled in a given time interval during the execution of a forced vital capacity. Conventionally, the times used are 0.5, 0.75, or 1 sec, symbolized $FEV_{0.5}$, $FEV_{0.75}$, $FEV_{1.0}$. These values are often expressed as a percent of the forced vital capacity, e.g. ($FEV_{1.0}$/VC) X 100.

Forced inspiratory vital capacity (FIVC): The maximal volume of air inspired with a maximally forced effort from a position of maximal expiration.

Forced vital capacity (FVC): Vital capacity performed with a maximally forced expiratory effort.

Functional residual capacity (FRC): The sum of RV and ERV (the volume of air remaining in the lungs at the end-expiratory position). The method of measurement should be indicated as with RV.

Gas exchange: Movement of oxygen from the alveoli into the pulmonary capillary blood as carbon dioxide enters the alveoli from the blood. In broader terms, the exchange of gases between alveoli and lung capillaries.

Gas exchange ratio (R): See RESPIRATORY QUOTIENT.

Gas trapping: Trapping of gas behind small airways that were opened during inspiration but closed during forceful expiration. It is a volume difference between FVC and VC.

Hematocrit (Hct): The percentage of the volume of red blood cells in whole blood.

Hemoglobin (Hb): A hemoprotein naturally occurring in most vertebrate blood, consisting of four polypeptide chains (the globulin) to each of which there is attached a heme group. The heme is made of four pyrrole rings and a divalent iron (Fe^{2+}-protoporphyrin) which combines reversibly with molecular oxygen.

Histamine: A depressor amine derived from the amino acid histidine and found in all body tissues, with the highest concentration in the lung; a powerful stimulant of gastric secretion, a constrictor of bronchial smooth muscle, and a vasodilator that causes a fall in blood pressure.

Hypoxemia: A state in which the oxygen pressure and/or concentration in arterial and/or venous blood is lower than its normal value at sea level. Normal oxygen pressures at sea level are 85-100 torr in arterial blood and 37-44 torr in mixed venous blood. In adult humans the normal oxygen concentration is 17-23 ml O_2/100 ml arterial blood; in mixed venous blood at rest it is 13-18 ml O_2/100 ml blood.

Hypoxia: Any state in which the oxygen in the lung, blood, and/or tissues is abnormally low compared with that of normal resting man breathing air at sea level. If the P_{O_2} is low in the environment, whether because of decreased barometric pressure or decreased fractional concentration of O_2, the condition is termed environmental hypoxia. Hypoxia when referring to the blood is termed hypoxemia. Tissues are said to be hypoxic when their P_{O_2} is low, even if there is no arterial hypoxemia, as in "stagnant hypoxia" which occurs when the local circulation is low compared to the local metabolism.

Inspiratory capacity (IC): The sum of IRV and TV.

Inspiratory reserve volume (IRV): The maximal volume of air inhaled from the end-inspiratory level.

Inspiratory vital capacity (IVC): The maximum volume of air inhaled from the point of maximum expiration.

Kilogram-meter/min (kg-m/min): The work performed each min to move a mass of 1 kg through a vertical distance of 1 m against the force of gravity. Synonymous with kilopond-meter/min.

Lung volume (V_L): Actual volume of the lung, including the volume of the conducting airways.

Maximal aerobic capacity (max $\dot{V}O_2$): The rate of oxygen uptake by the body during repetitive maximal respiratory effort. Synonymous with maximal oxygen consumption.

Maximum breathing capacity (MBC): Maximal volume of air which can be breathed per minute by a subject breathing as quickly and as deeply as possible. This tiring lung function test is usually limited to 12-20 sec, but given in liters (BTPS)/min. Synonymous with maximum voluntary ventilation (MVV).

Maximum expiratory flow ($\dot{V}_{max\ x}$): Forced expiratory flow, related to the total lung capacity or the actual volume of the lung at which the measurement is made. Modifiers refer to the amount of lung volume remaining when the measurement is made. For example:

$\dot{V}_{max\ 75\%}$ = instantaneous forced expiratory flow when the lung is at 75% of its TLC.

$\dot{V}_{max\ 3.0}$ = instantaneous forced expiratory flow when the lung volume is 3.0 liters

Maximum expiratory flow rate (MEFR): Synonymous with $FEF_{200-1200}$.

Maximum mid-expiratory flow rate (MMFR or MMEF): Synonymous with $FEF_{25-75\%}$.

Maximum ventilation (max $\dot{V}_E$): The volume of air breathed in one minute during repetitive maximal respiratory effort. Synonymous with maximum ventilatory minute volume.

Maximum voluntary ventilation (MVV): The volume of air breathed by a subject during voluntary maximum hyperventilation lasting a specific period of time. Synonymous with maximum breathing capacity (MBC).

Methemoglobin (MetHb): Hemoglobin in which iron is in the ferric state. Because the iron is oxidized, methemoglobin is incapable of oxygen transport. Methemoglobins are formed by various drugs and occur under pathological conditions. Many methods for hemoglobin measurements utilize methemoglobin (chlorhemiglobin, cyanhemiglobin).

Minute ventilation ($\dot{V}_E$): Volume of air breathed in one minute. It is a product of tidal volume (V_T) and breathing frequency (f_B). See VENTILATION.

Minute volume: Synonymous with minute ventilation.

Mucociliary transport: The process by which mucus is transported, by ciliary action, from the lungs.

Mucus: The clear, viscid secretion of mucous membranes, consisting of mucin, epithelial cells, leukocytes, and various inorganic salts suspended in water.

Nasopharyngeal: Relating to the nose or the nasal cavity and the pharynx (throat).

Nitrogen oxides: Compounds of N and O in ambient air; i.e., nitric oxide (NO) and others with a higher oxidation state of N, of which NO_2 is the most important toxicologically.

Nitrogen washout (ΔN_2, dN_2): The curve obtained by plotting the fractional concentration of N_2 in expired alveolar gas vs. time, for a subject switched from breathing ambient air to an inspired mixture of pure O_2. A progressive decrease of N_2 concentration ensues which may be analyzed into two or more exponential components. Normally, after 4 min of pure O_2 breathing the fractional N_2 concentration in expired alveolar gas is down to less than 2%.

Normoxia: A state in which the ambient oxygen pressure is approximately 150 ± 10 torr (i.e., the partial pressure of oxygen in air at sea level).

Oxidant: A chemical compound that has the ability to remove, accept, or share electrons from another chemical species, thereby oxidizing it.

Oxygen consumption ($\dot{V}O_2$, $\dot{Q}O_2$): Rate of oxygen uptake of organisms, tissues, or cells. Common units: ml O_2 (STPD)/(kg·min) or ml O_2 (STPD)/(kg·hr). For whole organisms the oxygen consumption is commonly expressed per unit surface area or some power of the body weight. For tissue samples or isolated cells $\dot{Q}_{O2}$ = µl O_2/hr per mg dry weight.

Oxygen saturation (SO_2): The amount of oxygen combined with hemoglobin, expressed as a percentage of the oxygen capacity of that hemoglobin. In arterial blood, SaO_2.

Oxygen uptake ($\dot{V}O_2$): Amount of oxygen taken up by the body from the environment, by the blood from the alveolar gas, or by an organ or tissue from the blood. When this amount of oxygen is expressed per unit of time one deals with an "oxygen uptake rate." "Oxygen consumption" refers more specifically to the oxygen uptake rate by all tissues of the body and is equal to the oxygen uptake rate of the organism only when the O_2 stores are constant.

Particulates: Fine solid particles such as dust, smoke, fumes, or smog, found in the air or in emissions.

Pathogen: Any virus, microorganism, or etiologic agent causing disease.

Peak expiratory flow (PEF): The highest forced expiratory flow measured with a peak flow meter.

Peroxyacetyl nitrate (PAN): Pollutant created by action of UV component of sunlight on hydrocarbons and NO_x in the air; an ingredient of photochemical smog.

Physiological dead space (V_D): Calculated volume which accounts for the difference between the pressures of CO_2 in expired and alveolar gas (or arterial blood). Physiological dead space reflects the combination of anatomical dead space and alveolar dead space, the volume of the latter increasing with the importance of the nonuniformity of the ventilation/perfusion ratio in the lung.

Plethysmograph: A rigid chamber placed around a living structure for the purpose of measuring changes in the volume of the structure. In respiratory measurements, the entire body is ordinarily enclosed ("body plethysmograph") and the plethysmograph is used to measure changes in volume of gas in the system produced 1) by solution and volatilization (e.g., uptake of foreign gases into the blood), 2) by changes in pressure or temperature (e.g., gas compression in the lungs, expansion of gas upon passing into the warm, moist lungs), or 3) by breathing through a tube to the outside. Three types of plethysmograph are used: a) pressure, b) volume, and c) pressure-volume. In type a, the body chambers have fixed volumes and volume changes are measured in terms of pressure change secondary to gas compression (inside the chamber, outside the body). In type b, the body chambers serve essentially as conduits between the body surface and devices (spirometers or integrating flowmeters) which measure gas displacements. Type c combines a and b by appropriate summing of chamber pressure and volume displacements.

Pneumotachograph: A device for measuring instantaneous gas flow rates in breathing by recording the pressure drop across a fixed flow resistance of known pressure-flow characteristics, commonly connected to the airway by means of a mouthpiece, face mask, or cannula. The flow resistance usually consists either of parallel capillary tubes (Fleisch type) or of fine-meshed screen (Silverman-Lilly type).

Pulmonary alveolar proteinosis: A chronic or recurrent disease characterized by the filling of alveoli with an insoluble exudate, usually poor in cells, rich in lipids and proteins, and accompanied by minimal histologic alteration of the alveolar walls.

Pulmonary edema: An accumulation of excessive amounts of fluid in the lung extravascular tissue and air spaces.

Pulmonary emphysema: An abnormal, permanent enlargement of the air spaces distal to the terminal nonrespiratory bronchiole, accompanied by destructive changes of the alveolar walls and without obvious fibrosis. The term emphysema may be modified by words or phrases to indicate its etiology, its anatomic subtype, or any associated airways dysfunction.

Residual volume (RV): That volume of air remaining in the lungs after maximal exhalation. The method of measurement should be indicated in the text or, when necessary, by appropriate qualifying symbols.

Resistance flow (R): The ratio of the flow-resistive components of pressure to simultaneous flow, in cm H_2O/liter per sec. Flow-resistive components of pressure are obtained by subtracting any elastic or inertial components, proportional respectively to volume and volume acceleration. Most flow resistances in the respiratory system are nonlinear, varying with the magnitude and direction of flow, with lung volume and lung volume history, and possibly with volume acceleration. Accordingly, careful specification of the conditions of measurement is necessary; see AIRWAY RESISTANCE, TISSUE RESISTANCE, TOTAL PULMONARY RESISTANCE, COLLATERAL RESISTANCE.

Respiratory cycle: A respiratory cycle is constituted by the inspiration followed by the expiration of a given volume of gas, called tidal volume. The duration of the respiratory cycle is the respiratory or ventilatory period, whose reciprocal is the ventilatory frequency.

Respiratory exchange ratio: See RESPIRATORY QUOTIENT.

Respiratory frequency (f_R): The number of breathing cycles per unit of time. Synonymous with breathing frequency (f_B).

Respiratory quotient (RQ, R): Quotient of the volume of CO_2 produced divided by the volume of O_2 consumed by an organism, an organ, or a tissue during a given period of time. Respiratory quotients are measured by comparing the composition of an incoming and an outgoing medium, e.g., inspired and expired gas, inspired gas and alveolar gas, or arterial and venous blood. Sometimes the phrase "respiratory exchange ratio" is used to designate the ratio of CO_2 output to the O_2 uptake by the lungs, "respiratory quotient" being restricted to the actual metabolic CO_2 output and O_2 uptake by the tissues. With this definition, respiratory quotient and respiratory exchange ratio are identical in the steady state, a condition which implies constancy of the O_2 and CO_2 stores.

Shunt: Vascular connection between circulatory pathways so that venous blood is diverted into vessels containing arterialized blood (right-to-left shunt, venous admixture) or vice versa (left-to-right shunt). Right-to-left shunt within the lung, heart, or large vessels due to malformations are more important in respiratory physiology. Flow from left to right through a shunt should be marked with a negative sign.

Specific airway conductance (SGaw): Airway conductance divided by the lung volume at which it was measured, i.e., normalized airway conductance. SGaw = Gaw/TGV.

Specific airway resistance (SRaw): Airway resistance multiplied by the volume at which it was measured. SRaw = Raw x TGV.

Spirograph: Mechanical device, including bellows or other scaled, moving part, which collects and stores gases and provides a graphical record of volume changes. See BREATHING PATTERN, RESPIRATORY CYCLE.

Spirometer: An apparatus similar to a spirograph but without recording facility.

Static lung compliance (C_{Lst}): Lung compliance measured at zero flow (breath-holding) over linear portion of the volume-pressure curve above FRC. See COMPLIANCE.

Static transpulmonary pressure (P_{st}): Transpulmonary pressure measured at a specified lung volume; e.g., P_{st}TLC is static recoil pressure measured at TLC (maximum recoil pressure).

Sulfur dioxide (SO_2): Colorless gas with pungent odor, released primarily from burning of fossil fuels, such as coal, containing sulfur.

STPD conditions (STPD): Standard temperature and pressure, dry. These are the conditions of a volume of gas at 0°C, at 760 torr, without water vapor. A STPD volume of a given gas contains a known number of moles of that gas.

Surfactant, pulmonary: Protein-phospholipid (mainly dipalmitoyl lecithin) complex which lines alveoli (and possibly small airways) and accounts for the low surface tension which makes air space (and airway) patency possible at low transpulmonary pressures.

Synergism: A relationship in which the combined action or effect of two or more components is greater than the sum of effects when the components act separately.

Thoracic gas volume (TGV): Volume of communicating and trapped gas in the lungs measured by body plethysmography at specific lung volumes. In normal subjects, TGV determined at end expiratory level corresponds to FRC.

Tidal volume (TV): That volume of air inhaled or exhaled with each breath during quiet breathing, used only to indicate a subdivision of lung volume. When tidal volume is used in gas exchange formulations, the symbol V_T should be used.

Tissue resistance (R_{ti}): Frictional resistance of the pulmonary and thoracic tissues.

Torr: A unit of pressure equal to 1,333.22 dynes/cm^2 or 1.33322 millibars. The torr is equal to the pressure required to support a column of mercury 1 mm high when the mercury is of standard density and subjected to standard acceleration. These standard conditions are met at 0°C and 45° latitude, where the acceleration of gravity is 980.6 cm/sec^2. In reading a mercury barometer at other temperatures and latitudes, corrections, which commonly exceed 2 torr, must be introduced for these terms and for the thermal expansion of the measuring scale used. The torr is synonymous with pressure unit mm Hg.

Total lung capacity (TLC): The sum of all volume compartments or the volume of air in the lungs after maximal inspiration. The method of measurement should be indicated, as with RV.

Total pulmonary resistance (R_L): Resistance measured by relating flow-dependent transpulmonary pressure to airflow at the mouth. Represents the total (frictional) resistance of the lung tissue (R_{ti}) and the airways (Raw). $R_L = R_{aw} + R_{ti}$.

Trachea: Commonly known as the windpipe; a cartilaginous air tube extending from the larynx (voice box) into the thorax (chest) where it divides into left and right branches.

Transpulmonary pressure (P_L): Pressure difference between airway opening (mouth, nares, or cannula opening) and the visceral pleural surface, in cm H_2O. Transpulmonary in the sense used includes extrapulmonary structures, e.g., trachea and extrathoracic airways. This usage has come about for want of an anatomic term which includes all of the airways and the lungs together.

Ventilation: Physiological process by which gas is renewed in the lungs. The word ventilation sometimes designates ventilatory flow rate (or ventilatory minute volume) which is the product of the tidal volume by the ventilatory frequency. Conditions are usually indicated as modifiers; i.e.,

$\dot{V}_E$ = Expired volume per minute (BTPS),
and
$\dot{V}_I$ = Inspired volume per minute (BTPS).

Ventilation is often referred to as "total ventilation" to distinguish it from "alveolar ventilation" (see VENTILATION, ALVEOLAR).

Ventilation, alveolar ($\dot{V}_A$): Physiological process by which alveolar gas is completely removed and replaced with fresh gas. Alveolar ventilation is less than total ventilation because when a tidal volume of gas leaves the alveolar spaces, the last part does not get expelled from the body but occupies the dead space, to be reinspired with the next inspiration. Thus the volume of alveolar gas actually expelled completely is equal to the tidal volume minus the volume of the dead space. This truly complete expiration volume times the ventilatory frequency constitutes the alveolar ventilation.

Ventilation, dead-space ($\dot{V}_D$): Ventilation per minute of the physiologic dead space (wasted ventilation), BTPS, defined by the following equation:

$$\dot{V}_D = \dot{V}_E(PaCO_2 - P_ECO_2)/(PaCO_2 - P_ICO_2)$$

Ventilation/perfusion ratio ($\dot{V}_A/\dot{Q}$): Ratio of the alveolar ventilation to the blood perfusion volume flow through the pulmonary parenchyma. This ratio is a fundamental determinant of the O_2 and CO_2 pressure of the alveolar gas and of the end-capillary blood. Throughout the lungs the local ventilation/perfusion ratios vary, and consequently the local alveolar gas and end-capillary blood compositions also vary.

Vital capacity (VC): The maximum volume of air exhaled from the point of maximum inspiration.

☆U.S. GOVERNMENT PRINTING OFFICE: 1986-646-116/40640